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BRITISH JOURNAL OF TUBERCULOSIS
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MASSIVE COLLAPSE OF THE LUNG IN BRONCHITIS AND BRONCHIAL ASTHMA

By C. M. Luke*

From the Sully Hospital, Glamorgan

The development of whole lung collapse from the accumulation of bronchial secretions is infrequent unless there has been preceding trauma or operation. This paper records the occurrence of a collapse of the left lung during an attack of acute bronchitis in an asthmatic adult. The development of atelectasis in asthma and bronchitis is reviewed.

Case Report

A young woman aged 18 was admitted to Sully Hospital on January 18, 1955, with a history of recurrent attacks of bronchial asthma since infancy, occurring more frequently during spring and autumn months. She had also been liable to attacks of bronchitis with wheezing during the winter. She had been free from asthma and bronchitis for four years, although at times noticed wheezing after severe exertion. She had had seasonal attacks of hay fever.

For six days prior to admission she had an increasingly severe irritating cough without sputum. Since the third day there had been dull pain and a tight sensation over the left chest. Dyspnœa developed during this period. There was no wheezing and no fever. Symptoms of a preceding upper respiratory tract infection were denied and there was no episode to suggest the inhalation of any foreign body.

Clinical Findings. Her general condition was good and she did not look ill, although she became breathless and cyanosed after spasms of coughing. The temperature was normal. The left chest was flat and immobile and the mediastinum was deviated to that side. The percussion note was impaired over the left lung and distant breath sounds were audible only over its upper third. There were no rhonchi.

Radiography showed loss of translucency of the left lung, complete in the lower and mid-zones (Fig. 1). The left hemidiaphragm was elevated and the mediastinum deviated to the left. There was marked herniation of the right lung into the left hemithorax (Fig. 2). The changes were consistent with a collapse of the left lung, complete except for a small area of aeration in the upper lobe. No radio-opaque foreign body could be demonstrated by tomography.

Investigation and Treatment. It was suspected that the collapse was due to accumulated bronchial secretions, and, although every effort was made to encourage coughing, the patient could expectorate nothing. Bronchoscopy was therefore performed shortly after admission. No foreign body was present. The left main bronchus contained thick mucopurulent secretions. This material was so viscid that even with strong suction it was not possible to aspirate it, but quantities of it were removed from the left main bronchus and the lower lobe bronchus using forceps. All distal bronchi visualised contained similar mucopus.

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(*Received for publication April* 12, 1956.)

The upper lobe fully aerated following bronchoscopy, but the lower lobe remained collapsed.

The patient was nursed in a tent into which oxygen was passed through a De Vilbiss nebuliser containing " Alevaire." Inhalations of 1 per cent. isoprenaline sulphate were given frequently and 4 grains (0·25 g.) of potassium iodide were given four-hourly as an expectorant. On this treatment the patient expectorated much thin watery sputum containing numerous blobs of grey mucus. The sputum was examined daily and no casts were seen.

Several specimens of sputa were cultured and grew normal respiratory flora, no particular organisms predominating. Paraffin sections of the secretions taken from the left main bronchus at bronchoscopy showed that they consisted entirely of mucous material with scattered clumps of leucocytes. These were predominantly pus cells, but in some areas were entirely eosinophils.

Course. Re-expansion of the lower lobe was not complete until January 31—*i.e.*, thirteen days after admission. This improvement was not attributed to the use of the aerosol detergent, but the patient was able to expectorate thin secretions with ease whilst the inhalations were continued.

Radiographs on February 4 revealed an irregular opacity in the left midzone extending downwards along the left cardiac border (Fig. 3). Lateral views showed that the shadows were in the lingula and in the apical segment of the lower lobe. The patient had no other symptoms at this time, although the temperature had risen to 100·4° F. (38° C.). Blood count showed an eosinophilia; W.B.C.s 15,200 per c.mm., of which 2,740 (18 per cent.) were eosinophils. Penicillin 500,000 units was given twice daily for four days. Radiological resolution was gradual, but became complete within five weeks. By this time the eosinophil count had slowly returned to normal. The E.S.R. on admission was 8 mm. per hour (Westergren), rose to 56 mm. per hour at the time of the appearance of the shadows, and was 10 mm. per hour one month later.

Other investigations were not contributory. Mantoux test was negative with 100 I.U. of P.P.D. Casoni test was negative. Several specimens of fæces were examined for parasitic ova with negative results. Routine skin tests to standard allergens were negative.

A bronchogram was subsequently done in September 1955. There was no significant bronchiectasis, although there was an irregular dilatation of a subsegmental bronchus in the posterior segment of the right upper lobe and in the anterior segment of the left upper lobe.

Radiographs taken when the patient was attending an asthma clinic in 1950 were later obtained. One film showed an area of consolidation in the right upper lobe. There was no displacement of the lesser fissure of mediastinum. She was well at the time although the E.S.R. was elevated. No white cell count was done. Radiographs were normal two weeks later.

This young woman had suffered from bronchial asthma for many years although she had been free from attacks for four years prior to this illness, which itself was not associated with wheezing. The condition preceding the collapse of the left lung was diagnosed as an acute bronchitis.

Discussion

Collapse of a lung occurs most commonly in bronchial carcinoma and is also seen in other conditions where there are gross anatomical changes in a main bronchus. In the absence of bronchial stenosis, whole lung collapse can

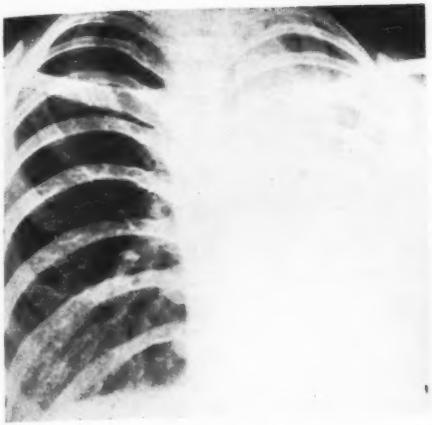

FIG. 1.—X-ray of chest showing an almost opaque left hemithorax consistent with collapse of the left lung.

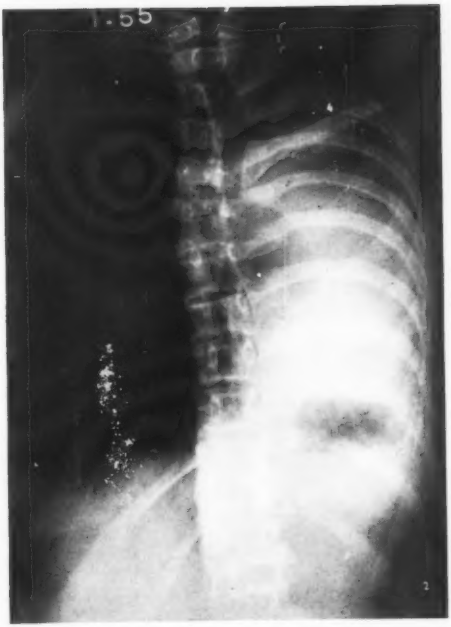

FIG. 2.—Showing marked herniation of the right lung into the left hemithorax.

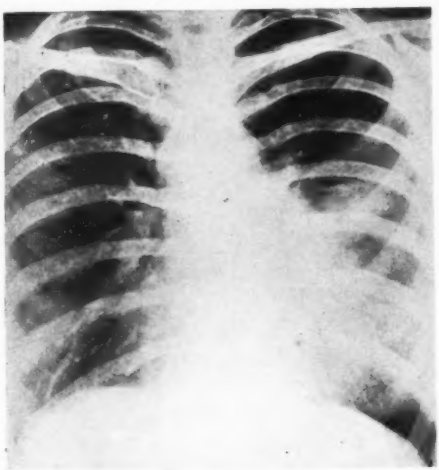

FIG. 3.—Showing considerable resolution (complete within 5 weeks).

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be due to bronchial obstruction by a foreign body or accumulated secretions. In adults it is rare for a bronchus proximal to the segmental divisions to be sufficiently occluded by retained secretions to cause collapse unless the efficiency of the cough mechanism is impaired by pain, narcosis or other factors. Post-operatively the direct effect of anæsthetic agents on the bronchi and their secretions is associated with impaired cilary activity (Palmer and Sellick, 1953). These factors operate together with those which impair the cough reflex so that accumulated secretions may occlude a major bronchus with resulting massive collapse.

The smaller calibre of the bronchi in young children enables plugs of viscid secretions to occlude major bronchi and lobar collapse may complicate any acute pulmonary infection in early infancy (Oswald, 1947). Lobar collapse has been recorded in 42 per cent. of a series of 150 cases of pertussis in children under the age of 7, although the collapse was partial in the majority of these (Lees, 1950).

Lung Collapse in Bronchitis

Although small areas of collapse occur commonly in chronic bronchitis (Reid, 1954), the occurrence of a collapsed lung during the course of an acute bronchitis is seldom reported, and lobar collapse in adults is equally uncommon. Maxwell (1937) recorded the complete collapse of a left lung during an attack of acute bronchitis in a woman aged 59, the lung re-expanding following the expectoration of a lump of thick mucus.

Obstruction of a major bronchus with resulting massive collapse may occur in so-called fibrinous or plastic bronchitis (Rakower, 1938; Woolley, 1953). The essential feature of this disease, which was first described by Galen, is the development of casts of the bronchial tree in association with an acute or chronic bronchitis. A detailed study of recorded cases was published by Bettmann (1902), and more recent cases have been reviewed by Walker (1920) and Woolley (1953). A preceding history of bronchial disease is usual, but a fatal attack may develop in a person who has not previously had respiratory symptoms (Johnstone, 1945). Although gross bronchial obstruction is present in severe cases, atelectasis is not common, presumably because individual bronchi are not completely occluded. Despite their macroscopic appearance, these casts do not contain true fibrin (Leggat, 1954). Similar casts may be expectorated in pulmonary tuberculosis, and have been seen in various other conditions such as rheumatic heart disease and typhoid fever. As casts may be found in the sputum of patients with bronchial asthma, it has been suggested that plastic bronchitis is closely related to this disease. The casts seen in asthma, however, are usually small and non-branching and, furthermore, a previous history of asthma is not a feature of typical cases of plastic bronchitis.

Lung Collapse in Asthma

Radiological evidence of transient atelectasis is common in asthmatic children. The changes are usually suggestive of segmental or lobular collapse, but lobar collapse also occurs frequently in infancy (Twining and Kerley, 1950). The abnormality may be detected when the patient is quite free from symptoms, but occurs more frequently during attacks of asthma. Even then it may

be a chance finding on routine radiography or fluoroscopy, but is more commonly found in association with severe prolonged attacks (Feinburg, 1946).

Whole lung collapse is rare even in children, and few cases have been reported. When this complication does occur, it usually develops during an asthmatic attack amd is accompanied by chest pain, an unproductive cough and severe dyspnœa. It can, however, develop during an acute respiratory infection not associated with clinical evidence of bronchial spasm. Therapeutic bronchoscopy is usually performed, but even without it complete re-expansion occurs, although radiological appearances may not return to normal for several weeks. The bronchoscopic findings are constant. Viscid, tenacious, mucoid or mucopurulent material is found occluding the main bronchus. Friedman and Moloney (1939) recorded the occurrence of collapse of the left lung in an asthmatic boy and found the bronchus filled with thick, yellow, tenacious secretions containing 90 per cent. eosinophils. The complication recurred seven months later. Occlusion of the left main bronchus by tenacious mucopus was reported by Maxwell (1937) in a boy of 13 in whom the lung collapsed during an asthmatic attack. Priest (1950) bronchoscoped a child of 9 who had a collapsed right lung and found thick mucoid secretions in the main bronchus. It is not recorded whether the collapse occurred during an asthmatic attack, but there was a previous history of asthma. Peshkin and Fineman (1931) recorded the complete collapse of a left lung in a boy of 9 who had not previously had respiratory symptoms. The main bronchus was filled with a mass of thick stringy material. Following this illness the child had recurrent asthma. In the case recorded by Kahn (1932) collapse of the right lung complicated an acute respiratory infection in a child aged 8 who had a previous history of bronchial asthma.

Although lobar collapse has been described (Clarke, 1930), no reference can be found to the complication of whole lung collapse developing in an adult with bronchial asthma. Rubin (1947) reported briefly on the occurrence of a massive atelectasis in a woman aged 36, but the radiological changes were not those usually associated with a collapsed lung, and in the bronchoscopic report the only comment was on the mucosal congestion seen in the main bronchus.

Pathogenesis of Atelectasis in Asthma

It appears that the bronchial secretions of asthmatics are at times so tenacious and viscous that ciliary movements and the expulsive efforts of coughing are not sufficient to remove them. The importance of ciliary action in expelling mucus is well known and has been clearly demonstrated experimentally by Hilding (1943), who proved that cilia alone can move mucus with sufficient power to build up a considerable negative pressure. The mucus occluding the bronchi in the case recorded here, however, was of such tenacity that direct aspiration could not remove it, and it was not surprising that ciliary movements could not expel it. It has been suggested that ciliary action is defective in asthma (Moore, 1925), but the evidence for this is not conclusive. Miller, Piness, Feingold and Friedman (1935) commented that bronchial narrowing due to muscular spasm and œdematous mucosal thickening is also a factor in the development of collapse in asthma. These changes, however, could have little effect on a main bronchus, with its large lumen and cartilaginous wall, and

it would seem unlikely that such a bronchus could be suddenly occluded by mucus if the lung beyond it were being normally aerated and no factors depressing the cough reflex were operating.

In most cases of whole lung or lobar collapse, the primary cause is occlusion of a major bronchus with absorption of air from the affected lung tissue. Secretions accumulate distal to the obstruction secondarily and their quantity is probably dependent upon the degree of associated infection. A different mechanism may, however, operate in the group of cases under discussion.

If viscid mucus occludes the smaller bronchi in several adjacent lobules and segments, massive atelectasis could occur, secretions later accumulating in the proximal bronchi because the expulsive effects of coughing are impaired by the distal atelectasis. With such a process of progressive occlusion of peripheral bronchi, a lobe or whole lung could become collapsed without the secretions in the main bronchus being the primary cause. In the smaller bronchi, spasm and and mucosal swelling could be additional factors in precipitating occlusion. The bronchoscopic findings and the persistence of lobar collapse following the removal of secretions in the main bronchus would suggest such a mechanism in the cases here recorded. The appearance at bronchoscopy in several other reported cases has been similar.

The tendency of these patients to secrete mucus of abnormal viscosity is also suggested by the higher incidence of post-operative collapse in asthmatics (Wilmer, Cobe and Lee, 1930). They can secrete mucus of this type in association with any respiratory infection, even when they are clinically free from asthma (Kahn, 1932), and that this tendency is constant in a particular individual is suggested by the repeated occurrence of atelectasis in certain patients (Friedman and Moloney, 1939; Rakower, Wayl and Halberstadt, 1955). This complication is quite distinct from the changes found in fatal cases of status asthmaticus. There the bronchi are filled with mucus which contains eosinophil polymorph leucocytes, together with detached ciliated bronchial epithelial cells, and although extensive bronchial plugging occurs, there is no significant degree of collapse (Houston de Navasquez and Trounce, 1953).

Pulmonary Eosinophilia in Asthma

Pulmonary infiltrations associated with blood eosinophilia may develop in bronchial asthma and may be present when there are no asthmatic symptoms (Hennell and Sussman, 1945).

There had been a transient consolidation in the right upper lobe in our patient previously, and the radiological changes which developed after the left lung re-expanded were accompanied by an eosinophilia which subsided as the opacity cleared.

Crofton, Livingstone, Oswald and Roberts (1952), in reviewing the association of pulmonary eosinophilia with bronchial asthma, commented that patients with asthma may develop an intercurrent pneumonia and have an eosinophilia associated with the original asthma. The cause of the various radiological changes that may develop in asthmatics is often obscure. Although atelectasis is common, the radiological appearances in many cases suggest that consolidation rather than collapse is the major factor in their production. Miller, Piness, Feingold and Friedman (1935) discussed the cause of such

opacities. They considered that although there was some bronchial obstruction and a degree of collapse, the main change was an exudation in the affected part of the lung which had an allergic basis. If such a process does occur there is no evidence that it is distinct from the exudation that has been described in these cases of asthma where the radiological changes before death were associated with a peripheral eosinophilia (Chafee, Ross and Gunn, 1942). Similar opacities could be caused by an aspiration pneumonia with an exudative process of bacterial origin. Unless the radiological changes are undoubtedly those of atelectasis, it is suggested that it is not possible to determine their exact cause in a given case, although if there is also a blood eosinophilia they will be attributed to "pulmonary eosinophilia."

Summary

A case is reported of massive collapse of the left lung in association with an acute respiratory infection in a young woman who had previously had bronchial asthma. The development of lung collapse in bronchitis and in asthma is reviewed.

The bronchial secretion of asthmatics may be abnormally tenacious under various circumstances. The mode of development of massive collapse in these patients is discussed. It is suggested that the proximal occlusion of a major bronchus may not be the primary factor.

The causes of other transient radiological lung changes which may be seen in asthma are discussed.

I wish to thank Dr. H. M. Foreman for his advice and encouragement in the preparation of this paper. The patient was admitted to hospital under his care. The bronchoscopy was performed by Mr. Dillwyn M. E. Thomas

REFERENCES

BETTMANN, M. (1902): *Amer. J. med. Sci.*, **123,** 304.
CHAFEE, F. H., ROSS, J. R., and GUNN, E. M. (1942): *Ann. intern. Med.*, **17,** 45.
CLARKE, J. A. (1930): *Arch. intern. Med.*, **45,** 624.
CROFTON, J. W., LIVINGSTONE, J. L., OSWALD, N. C., and ROBERTS, A. T. M. (1952): *Thorax*, **7,** 1.
FEINBURG, S. M. (1946), in "Allergy in Practice," p. 405, Year Book Publishers, Chicago.
FRIEDMAN, T. B., and MOLONEY, C. J. (1939): *Amer. J. Dis. Child.*, **58,** 237.
HENNELL, H., and SUSSMAN, M. L. (1945): *Radiology*, **44,** 328.
HILDING, A. C. (1943): *Ann. Otol., Rhin. and Laryng.*, **52,** 816.
HOUSTON, J. C., DE NAVASQUEZ, S., and TROUNCE, J. R. (1953): *Thorax*, **8,** 207.
JOHNSTONE, D. F. (1945): *Guy's Hosp. Gaz.*, **59,** 2.
KAHN, I. S. (1932): *Tex. St. J. Med.*, **28,** 416.
LEES, A. W. (1950): *Brit. med. J.*, **2,** 1138.
LEGGAT, P. (1954): *Dis. Chest*, **26,** 464.
MAXWELL, J. (1937): *St. Bart's Hosp. Rep.*, **70,** 183.
MILLER, H., PINESS, G., FEINGOLD, B. F., and FRIEDMAN, T. B. (1935): *J. Pediat.*, **7,** 768.
MOORE, W. F. (1925): *Amer. J. med Sci.*, **169,** 799.
OSWALD, N. C. (1947): *Proc. roy. Soc. Med.*, **40,** 736.
PALMER, K. N. V., and SELLICK, B. A. (1953): *Lancet*, **1,** 164.
PESHKIN, M. M., and FINEMAN, A. H. (1931): *Amer. J. Dis. Child.*, **42,** 590.
PRIEST, R. E. (1950): *Ann. Otol., Rhin. and Laryng.*, **59,** 889.
RAKOWER, J. (1938): *Presse Méd.*, **46,** 1116.
RAKOWER, J., WAYL, P., and HALBERSTADT, H. (1955): *Dis. Chest*, **27,** 573.
REID, L. McA. (1954): *Lancet*, **1,** 275.
RUBIN, I. H. (1947) in "Diseases of Chest," p. 368, W. B. Saunders, London.
TUCKER, G. (1931): *Arch. Otolaryng.*, **13,** 315.
TWINING, E. W., and KERLEY, P. (1950) in "X-ray Diagnosis," vol. 2, p. 318. Ed. S. C. Shanks and P. Kerley. London: H. K. Lewis and Co.
WILMER, H. B., COBE, H. M., and LEE, W. E. (1930): *Ann. Surg.*, **91,** 651.
WOOLLEY, P. E. (1953): *Thorax*, **8,** 301.

SPONTANEOUS HÆMOPNEUMOTHORAX

A REPORT OF THREE CASES

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Spontaneous hæmopneumothorax is potentially a serious condition with a high morbidity and mortality rate.

About 150 cases of spontaneous hæmopneumothorax have been reported. Recently it has been regarded as a surgical emergency, being treated by thoracotomy with transfusion when necessary. In less severe cases the conservative measures of repeated aspiration, blood transfusion and instillation of fibrinolytic enzymes still have a place.

This paper reports three cases of spontaneous hæmopneumothorax, two treated by early thoracotomy and the third by repeated aspirations. All cases returned to normal function with complete re-expansion of the lungs.

Case 1. A male aged 28 years had an acute onset of severe generalised abdominal pain and shortness of breath twelve hours previously. This pain was aggravated by movement and deep breathing. The only relevant past history was of mild dyspepsia. He was orthopnœic, pale and shocked. Pulse 120, respirations 46, apyrexial, B.P. 120/80.

In the chest there was mediastinal shift to the right, movements were diminished on the left, percussion note impaired at the left base but hyperresonant in the upper and mid-zones with absent tactile fremitus and vocal resonance and diminished air entry. The abdominal wall was rigid and nil else abnormal was found.

Investigations: E.S.R. 8 mm./hr. Hæmoglobin 70%, W.B.C. 13,800 with 70% polymorphs.

Chest X-ray: Left pneumothorax with some fluid at the left base (Fig. 1).

Chest Aspiration: 140 ml. of blood removed and release of pneumothorax attempted.

He was given a blood transfusion of 2 pints with benefit. The next day he had deteriorated in that he was dyspnœic, the blood pressure had fallen and the pulse rate had increased. A further transfusion of 4 pints of blood was given. This was followed by thoracotomy and about 6 pints of dark fluid, blood with clots, were removed from the left pleural cavity. No source of bleeding was found, but there were a few emphysematous bullæ at the apex of the lung and some adhesions between the lung and the pleura. The lung was fully re-expanded with positive pressure. The post-operative period was uneventful, the patient being discharged twelve days after admission. One year later he had had no further trouble and the chest X-ray was normal (Fig. 2).

Case 2.—A healthy male aged 23 years had sudden onset of sharp pain in the left shoulder and back which radiated down his arm and left side. This was followed by breathlessness which became acute twenty-four hours later when he was admitted to hospital.

He was pale, dyspnœic, pulse 120, respirations 40, apyrexial, B.P. 100/70.

(*Received for publication March* 27, 1956.)

In the chest there was mediastinal displacement to the right, and signs of a hydropneumothorax on the left side. There were no other abnormal physical signs.

Investigations: E.S.R. 34 mm./hr., Hb. 70%, W.B.C. 10,500 with 65% polymorphs.

Chest X-ray: Gross displacement of the mediastinum to the right, a completely atelectatic left lung with a large collection of air in the left pleura and a fluid level reaching the neck of the tenth rib.

Chest Aspiration: 3 pints of blood were removed from left pleural cavity. A blood transfusion of 6 pints was given. Twenty-four hours later a further 250 ml. of blood were removed from his chest and his general condition seemed to improve, but forty-eight hours later there were signs of further bleeding in his chest.

He was given further blood transfusions. At this stage thoracocentesis using an intercostal catheter in the second interspace anteriorly was instituted. There was a rush of air on removing the trocar and subsequently over a pint of bloody fluid was drained. His general condition improved dramatically. The mediastinum returned to its central position, but the apex of the lung did not rise above the neck of fifth rib and the hæmothorax persisted.

An exploratory thoracotomy was performed—the chest was entered through the bed of the sixth rib. About a pint of fibrin clot was removed from the pleura and a decortication was carried out. No bleeding point or air leak was found and the underlying lung appeared healthy. Post-operatively the lungs re-expanded satisfactorily. The patient was discharged with a normal chest X-ray after sixteen days.

Case 3.—A healthy male, aged 23 years, was admitted complaining of acute left-sided pleuritic pain of six hours' duration. This has been followed by left shoulder tip pain and increasing dyspnœa.

He was shocked, dyspnœic, apyrexial; pulse 120, respiration 40, B.P. 95/60.

In the chest there was mediastinal shift to the right and signs of a left hydropneumothorax.

Investigations: E.S.R. 40 mm./hr., Hb. 80%, W.B.C. 17,000 with 90% polymorphs.

Chest X-ray: Left pneumothorax with fluid on the left side (Fig. 3).

Chest Aspiration: 1¾ pints of blood removed. A transfusion of 4 pints of blood was given with benefit. Chest aspiration was performed daily for a week with removal of 600 ml. on each occasion, and penicillin with streptokinase were given intra-pleurally.

Patient was discharged six weeks later with residual pleural thickening and limitation of diaphragmatic movements on the left side. Eighteen months later he was asymptomatic and without clinical or radiological signs (Fig. 4).

Discussion

The exact source of bleeding in spontaneous hæmopneumothorax remains a matter of speculation. The generally accepted concept is that hæmorrhage results from rupture of subpleural bullæ and adhesions (Pitt, 1900; Hopkins, 1937; Hartzell, 1942). Cunningham (1950) at 21 necropsies found no source of bleeding in 18 cases and torn adhesions only in 3 cases. In cases who had immediate thoracotomies the findings were similar (Hansen, 1949; Myers *et al.*, 1951; Ross *et al.*, 1953). Less likely causes are rupture of a tuberculous focus or a subpleural cyst in association with aberrant lung tissue.

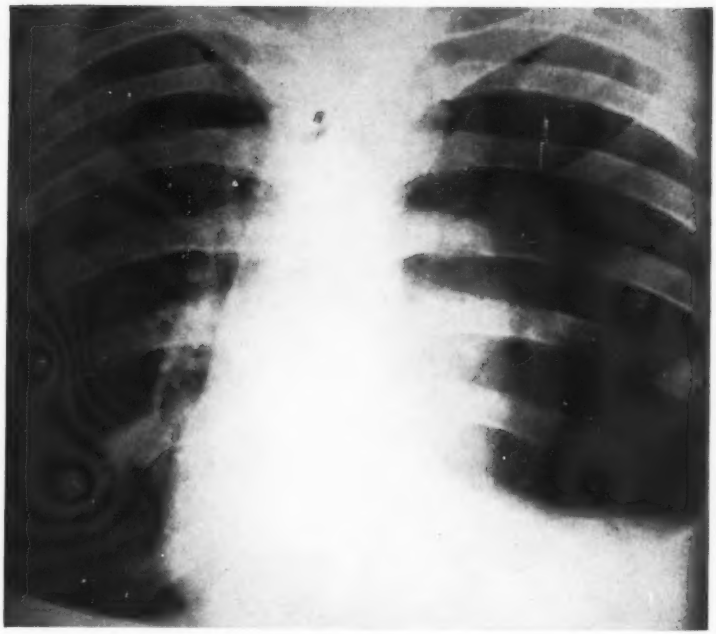

FIG. 1.—(Case 1.) Spontaneous Hæmopneumothorax. On admission.

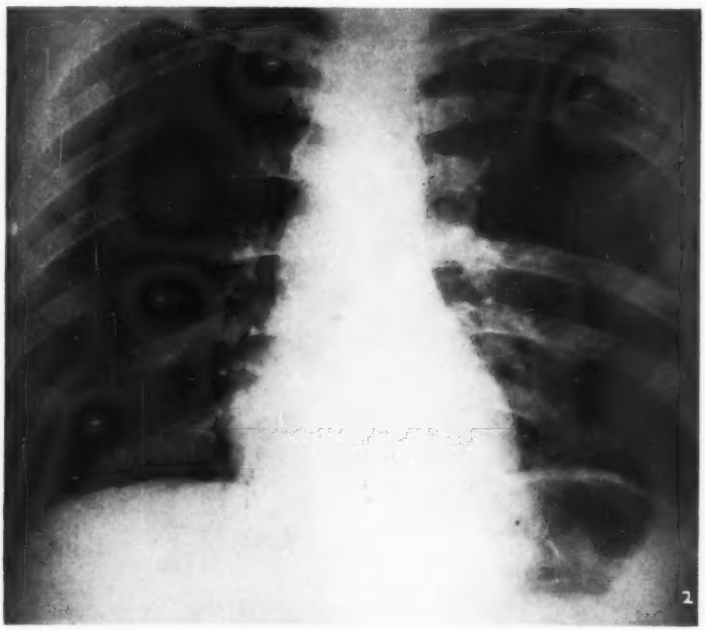

FIG. 2.—(Case 1.) On discharge 12 days later X-ray chest showing recovery.

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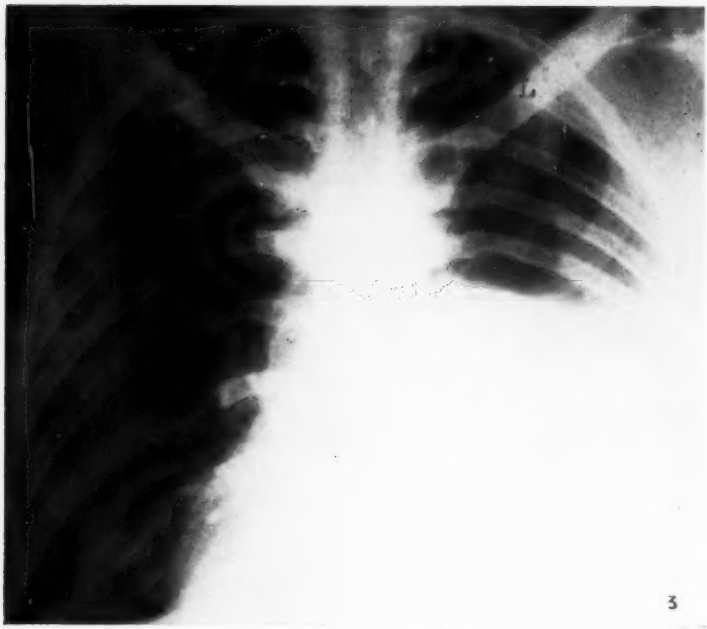

FIG. 3.—(Case 3.) Spontaneous Hæmopneumothorax. On admission.

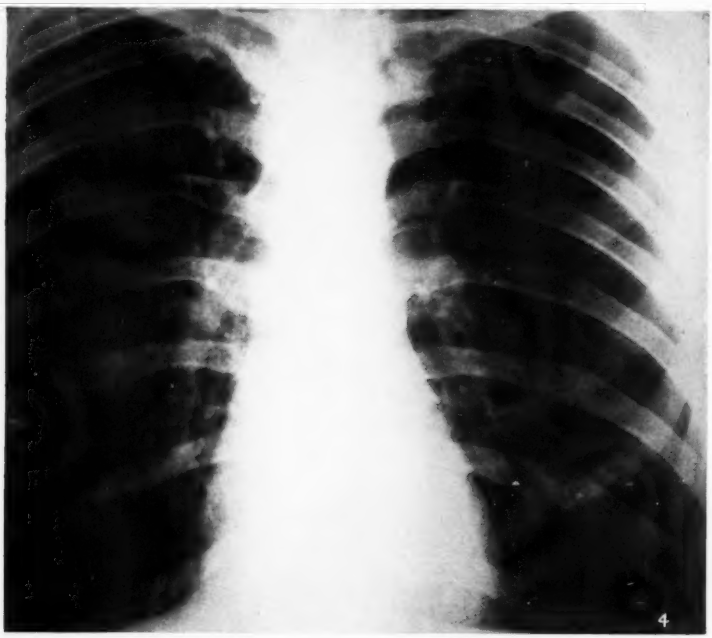

FIG. 4.—(Case 3.) On discharge 6 weeks later X-ray chest showing recovery.

Perry (1939) and Hyde and Hyde (1951) found it quite exceptional for pulmonary tuberculosis to develop later in their cases. The causative lesion in our first case was probably rupture of an apical emphysematous bulla which, with the reduction of intra-thoracic pressure after thoracocentesis, had continued to bleed, necessitating an emergency thoracotomy. In the other two cases it remains obscure but is unlikely to be tuberculosis because of the satisfactory follow-up.

The typical clinical picture in cases of hæmopneumothorax is an acute onset resembling spontaneous pneumothorax with associated signs of internal hæmorrhage and pleural effusion. Pain is usually pleural in nature but may be atypical as displayed by case 1, which simulated a perforated peptic ulcer. There is commonly a slight pyrexia, raised sedimentation rate and leucocytosis.

There are differing views on treatment. Thoracocentesis used to be delayed, as it was thought that pressure of blood in the pleural cavity would prevent further bleeding. Jones and Gilbert (1936), Waring (1945), Hyde and Hyde (1951), treated their cases conservatively by repeated aspirations and blood transfusions, and the average period for recovery was two to three months. In such cases an overall mortality of 15 to 25 per cent. has been reported (Myers, Johnston and Bradshaw, 1951; Ross, 1952). To prevent fibrin deposition and subsequent need for decortication fibrinolytic enzymes may be instilled intrapleurally (Sherry *et al.*, 1950; Read and Berry, 1950; Belly and Frelick, 1952). Sellors (1945), Tuttle-Langston and Crowly (1947) favoured early thoracocentesis until the pleural cavity was dry. It is now suggested that if bleeding continues or recurs early thoracotomy should be performed (Hansen, 1949; Ross *et al.*, 1951; Myers, 1951; Borrie, 1953; Clyne and Hunter, 1955; and Calvert and Smith, 1955).

Our experience supports the value of surgery being performed early, as although case 3 managed on conservative régime finally did very well, his hospital stay was much longer. We would agree a massive and uncontrolled intrapleural hæmorrhage should be treated as a surgical rather than a medical emergency.

Summary

(1) Three cases of spontaneous hæmopneumothorax are reported.

(2) The ætiology, clinical picture and the complications are discussed.

(3) The management of three cases, one by repeated aspirations and the other two by immediate thoracotomy, is described and discussed.

We wish to thank Mr. Bates, Mr. G. Flavell and Mr. A. Small for their help and permission to publish these cases.

REFERENCES

Borrie, J. (1953): *Brit. med. J.*, **2**, 16.
Calvert, R., and Smith, L. (1955): *Thorax*, **10**, 64.
Clyne, A. J., and Hunter, F. H. D. (1955): *Brit. med. J.*, **1**, 1058.
Cunningham, J. A. K. (1950): *N. Z. med. J.*, **49**, 708.
Hansen, J. L. (1949): *Acta med. scand.*, **132**, 517.
Hyde, L., and Hyde, B. (1951): *Amer. Rev. Tuberc.*, **63**, 417.
Kjaergaard, H. (1932): *Acta. med. Scand.*, Suppl. 43.
Myers, R. T., Johnston, F. R., and Bradshaw, H. H. (1951): *Ann. Surg.*, **133**, 413.
Perry, K. M. A. (1939): *Quart. J. Med.*, **8**, 1.
Ross, C. A. (1952): *J. thorac. Surg.*, **23**, 282.
Sellors, T. H. (1945): *Lancet*, **1**, 143. (1951): "Brit. Encyclopædia of Medical Practice," vol. 6, p. 177.

BRONCHIAL CARCINOMA

A REVIEW OF 116 CASES

By V. Ursula Lutwyche

From the Willesden Chest Clinic

The recent increase in the incidence of bronchial carcinoma has caused widespread concern. In 1953 for the first time the number of deaths from this condition in England and Wales exceeded those due to pulmonary tuberculosis, while in 1954 they were more than double those due to the latter condition. In the latter year no less than 30 per cent. of the total male deaths from cancer (47,319) were certified as due to carcinoma of the lung and bronchus. It must now in fact be regarded as one of the most common diseases affecting middle-aged and elderly men. It is for this reason that it has been considered worth while to review briefly those cases of bronchial carcinoma seen at the Willesden Chest Clinic during the last few years. These cases and the conclusions reached are in no way different from those reported by other writers, but it is hoped none the less that they may be of interest and serve as a reminder of the frequency of the disease and of the ease with which the correct diagnosis may not be made until too late to benefit the patient.

Clinical Material

A search of the records during the four-year period June 1950-June 1954 revealed 104 patients diagnosed as suffering from bronchial carcinoma; in addition records were available for 12 patients during the preceding four years 1946-50, making a total of 116 patients. In 86 of these (74 per cent.) the diagnosis was confirmed either by a positive biopsy at bronchoscopy, at thoracotomy or at autopsy, whereas in the remaining 30 cases (26 per cent.) definite proof was lacking. A review of the history, symptoms, radiological appearances and subsequent course of the disease in these 30 patients, combined with suggestive bronchoscopic evidence in 14 cases, leaves little doubt that the diagnosis was correct.

Mode of Access to Chest Clinic

Of the 116 patients seen at the Willesden Chest Clinic, 106 were referred by their general practitioners on account of symptoms, 3 were referred following miniature mass radiography, and 2 were examined as contacts of relatives suffering from pulmonary tuberculosis. In 4 cases bronchial carcinoma was seen to develop in known tuberculous patients, and in 1 case a bronchial carcinoma developed in a man suffering from sarcoidosis.

Sex

Of the 116 patients, 104 were men and 12 were women (ratio 8·6 : 1).

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Age

Table 1 shows the age incidence. It may be noted that 25 (21 per cent.) were under 50 years of age and 5 were under 40.

TABLE 1

Age in years	30-39	40-49	50-59	60-69	70-79
No.	5	20	42	41	8

Smoking Habits

In 22 cases no record is available of smoking habits; of the remaining 94 patients 69 (75 per cent.) smoked more than fifteen cigarettes daily, while only 2 (1·7 per cent.) were non-smokers.

Symptoms

As mentioned above, the majority of patients were referred to the chest clinic on account of symptoms. Table 2 shows the chief presenting symptoms in order of frequency.

TABLE 2

Symptoms	*Number of patients*
Cough	75
Hæmoptysis	65
Chest pain	59
Dyspnœa	51
Recent febrile illness	51
Loss of weight	41
Lassitude	29
Wheezing	12

Cough

It may be noted that whereas nearly all the patients complained of some cough, in some cases for a number of years, in 75 (64·6 per cent.) it had recently become of sufficient importance for the patient to consult his doctor. In many cases it had recently changed in character; 11 patients complained it was no longer relieved by the doctor's medicine, 4 complained of recent difficulty in bringing up sputum, while 3 complained of the sudden onset of profuse expectoration of frothy white sputum, whereas previously the cough had been unproductive. In a certain number of cases the patient remarked on the effect on cough of change of posture; in some cases it was stated to be worse on lying down or to be aggravated by lying on one one or other side, usually on the side of the lesion. Several patients complained of an uncontrollable cough which occurred in spasms. In 12 cases the cough was stated to have become considerably worse since an attack of influenza or bronchitis three or four weeks previously.

Hæmoptysis

A hæmoptysis or blood-stained sputum appeared to be the second most common symptom, 65 patients giving such a history. In most cases the amount of blood was small and in many took the form merely of staining of sputum.

Chest Pain

Fifty-nine patients complained of pain in the chest; in 44 the pain was experienced on the same side as the lesion, in 3 on the opposite side, while in the remainder it was situated either retrosternally or posteriorly between the scapulæ. In several cases pain was exaggerated at night when the patient was lying on the affected side, relief being obtained by change of posture. In some cases the pain was pleural in character, in others it was deep-seated. In many cases it was aggravated by coughing, and in many cases both pain and cough were said to date from a respiratory illness a few weeks previously.

Dyspnœa

This was a prominent symptom in 51 patients; in the majority it was present only on exertion, but some complained of breathlessness at night and of having to sleep with several pillows. This latter fact was probably responsible for causing more than one general practitioner to assume that the symptoms were cardiac in origin.

Recent Febrile Illness

No less than 51 patients (44 per cent.)—*i.e.*, nearly half the total number—gave a history of a recent respiratory infection a few weeks previously and in many instances dated their symptoms from this time.

Loss of Weight

Forty-one patients complained of loss of weight. This should be regarded as a late symptom, and in none of these 41 patients was the condition operable.

Wheezing

Twelve patients complained of the recent onset of wheezing, in some cases being able to point to the side of the chest affected.

Physical Signs in the Lungs

In a large number of patients no abnormal physical signs were present. In a few advanced cases where a large pleural effusion was present, or collapse of one lung had occurred, the physical signs of this condition were obvious. In the remainder the chief abnormality to be detected was either a diminution of air entry over one area of the lung fields, or a localised wheeze.

Blood Sedimentation Rate

This was found to be of little help in diagnosis, as in many early cases it was within normal limits. In 18 (24 per cent.) cases the blood sedimentation rate was less than 10 mm. in one hour. In 40 cases no record was available. (See Table 3.)

TABLE 3

B.S.R. in mm.	*Less than 5*	*5-9*	*10-14*	*15-19*	*20-29*	*30-49*	*50-70*	*Greater than 70*
No. of patients	10	8	10	2	18	12	6	10

Bronchoscopy

One hundred and eight of the 116 underwent bronchoscopy. In 67 of these (62 per cent.) the diagnosis was confirmed on bronchoscopy, histological proof being obtained by biopsy in 57 and a carcinoma being seen but no biopsy taken in the remaining 10. It is of interest to note that in 1 case in which a positive biopsy was obtained no abnormality was visible bronchoscopically, but a blind biopsy taken from the depths of the right upper lobe bronchus revealed a squamous carcinoma. In another case a positive biopsy was obtained from a small lesion of the bronchial muscosa four weeks after a previous bronchoscopy which had revealed no abnormality. Both these patients underwent pneumonectomy and both are alive and working seven and a half and four years later respectively. In 23 patients stenosis or distortion of the bronchi was reported, and in 1 patient blood was seen coming from the bronchial orifice of the affected lobe. In 2 patients, owing to technical difficulties, an adequate view was not obtained. In 15 patients (14 per cent.) bronchoscopy revealed no abnormality.

Delay in Diagnosis

In 37 of the 116 patients—*i.e.* nearly 33 per cent.—there was gross delay in diagnosis. In 17 patients there was undue delay between the onset of symptoms and reference to the chest clinic. In some cases this was due to delay in seeking advice from the general practitioner, and in some cases the general practitioner had disregarded the significance of the symptoms. In 18 patients a wrong diagnosis had initially been made. Thus 7 patients were thought to be suffering from unresolved pneumonia, and 8 from pulmonary tuberculosis. Two patients referred for X-ray examination on account of hæmoptysis had a normal chest radiograph at that time, but were subsequently found to have a bronchial carcinoma twenty months and two years later respectively. A review of the history leaves little doubt that this condition must have been present when they were first seen. In two other patients the symptoms were thought by the general practitioner to be cardiac in origin, and they had been treated on this assumption for some months.

Treatment

Thirty-six patients (31 per cent.) underwent thoracotomy and 24 of these resection; 22 pneumonectomy and 2 lobectomy. Of these 24 patients 9 are still surviving. Table 4 shows the number of years since operation of these patients.

TABLE 4

Years since operation	8	7	6	5	4	3	2	1
Number of patients	1	4	4	4	6	7	8	9

Discussion

From this review of 116 cases of bronchial carcinoma several points of interest emerge. Firstly the frequency of misdiagnosis. In no fewer than 18 of these 116 patients the condition was at first wrongly diagnosed and thereby valuable

time lost. Many authors have commented on how easy it is for the true diagnosis to be missed. Bryson and Spencer (1951) noted that in a review of 804 cases, in all of whom autopsy was performed, and where the original radiograph or report was available, the initial error in diagnosis was no less than 60·4 per cent. They pointed out how often secondary pathological changes in the lungs may obscure the primary condition, and stress the importance of always considering bronchial carcinoma as a possible diagnosis in any man over the age of 40.

The importance of not placing too much importance on a negative bronchoscopy cannot be overstressed. In 15 patients of the present series no abnormality was seen on bronchoscopy. As noted above, the presence of a carcinoma was revealed in one of these patients by a blind biopsy, and in another by repeating the examination after an interval of four weeks. In another patient whose radiograph gave the appearance of a mass at the left hilum, a bronchial carcinoma was confirmed at thoracotomy only nine days after bronchoscopy had revealed no abnormality. Churchill (1948) remarked that in at least 30 per cent. of cases of bronchial carcinoma bronchoscopy was of little help in the diagnosis, while Reiss *et al.* (1952) in their series of 70 patients noted that a positive bronchoscopy was obtained in only 53 per cent. of those investigated. Similarly undue reliance should not be placed on a negative biopsy report, if the other findings are suggestive of a carcinoma. In 9 of the present series the pathological report gave no evidence of a neoplastic condition, while in several others it was inconclusive.

Hæmoptysis is generally recognised to be a common symptom of bronchial carcinoma and was present in 65 patients of this series. As noted above, 2 of these patients had a normal chest radiograph when first seen. MacHale (1953) reported the results of bronchoscopic examination in 109 patients in whom the first symptom was a hæmoptysis. In 71 of these patients no definite lesion was visible in the radiograph, but in 4 a tumour was visible on bronchoscopy. Victor (1955) considers that in 20 per cent. of cases of early bronchial carcinoma no abnormality may be obvious on the X-ray, in some cases due to concealment by normal structures.

Wheezing is a symptom which may be too easily ignored; a localised wheeze which persists on coughing, however, should always be considered of significance. Johnston *et al.* (1954), describing the physical signs which may be present in bronchial obstruction, found that a localised wheeze was present in 40 (24 per cent.) of 117 cases of bronchial carcinoma. Flavell (1952) reported the case of a man who underwent thorough investigation on account of a persistent wheeze in the upper part of the left chest; X-ray, bronchogram and bronchoscopy were all reported as showing no abnormality. One year later, however, he was found to have a carcinoma of the anterior segment of the left upper lobe. A review of the previous bronchogram then showed that failure to fill of this segmental bronchus had been missed.

Although loss of weight is a recognised symptom of bronchial carcinoma, it is perhaps not sufficiently realised that a gain in weight can occur despite the presence of a carcinoma, when the patient's activities are limited. In 3 patients of the present series who were thought to be suffering from pulmonary tuberculosis considerable gain in weight occurred during a period of bed rest, and with-

out the use of anti-tuberculous drugs. With the use of chemotherapy, the gain in weight may be spectacular. Thus 1 patient (not included in the present series) is known to have gained over 2 stones in weight during the five months he spent in a tuberculosis ward. He died four weeks after discharge from hospital as a quiescent case of pulmonary tuberculosis, of a bronchial carcinoma completely obstructing the right upper lobe bronchus and complicated by a large pleural effusion.

The danger of missing the diagnosis of bronchial carcinoma due to upper lobe lesions being considered to be tuberculous has been noted by several authors. Overholt (1943) observed that in a series of 165 patients with bronchial carcinoma 104 were at first incorrectly diagnosed, and of these 40 were considered to be suffering from pulmonary tuberculosis. Scatchard (1944) pointed out the danger of accepting a diagnosis of pulmonary tuberculosis when the lesion is unilateral, cavitation is present, and tubercle bacilli cannot be demonstrated in the sputum. The present author (1954) described 5 such cases incorrectly diagnosed as tuberculous in spite of persistent failure to find tubercle bacilli in the sputum.

The frequency with which the symptoms of a bronchial carcinoma appear to date from a respiratory infection which fails to clear completely has been observed by many workers and was a prominent feature in many patients of the present series. Jewett (1952) noted that one-third of his series of 150 patients gave such a history and pointed out the danger of a false sense of security being engendered by an apparent response to antibiotics. McGibbon *et al.* (1939) stressed the importance of bronchoscopic examination of any patient with a so-called unresolved pneumonia if radiological improvement failed to occur within two weeks.

Conclusions

The increasing frequency of bronchial carcinoma makes the problem of early diagnosis of paramount importance. The number of patients diagnosed with the disease in an operable stage and with a reasonably good prognosis is still small. It is essential, if better results are to be achieved, that this diagnosis should constantly be borne in mind. In the words of Reiss *et al.* (1952), "cancer of the lung should be given primary consideration whenever one is confronted with an unexplained pulmonary lesion." General practitioners should be encouraged to refer patients with a suggestive history for X-ray of chest, however slight the symptoms, and consultant physicians should keep such patients under close observation even if the radiograph is normal. In particular no male patient over the age of 40, whose sputum has failed to reveal tubercle bacilli, should be diagnosed as suffering from pulmonary tuberculosis until the presence of a bronchial carcinoma has been excluded, if necessary by thoracotomy. Neville and Munz (1955) speak truly when they say, "Too many patients were treated in the past and unfortunately too many are even being treated to-day for an inflammatory lesion in the lung while carcinoma is the underlying cause. Antibiotics will clear the peripheral manifestations but will do nothing for the neoplasm."

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REFERENCES

Bryson, C. C., and Spencer, H. (1951): *Quart. J. Med. New Series, XX*, **78**, 173.
Churchill, E. D. (1948): *J. Amer. med. Ass.*, **137**, 456.
Flavell, G. (1952): *Lancet*, **11**, 884.
Jewett, J. S. (1952): *Dis. Chest*, **12**, 699.
Johnston, R. N., *et al.* (1954): *Brit. med. J.*, **1**, 799.
Lutwyche, V. U. (1954): *Lancet*, **1**, 693.
McGibbon, J. E. G. *et al.* (1939): **2**, 183.
MacHale, S. J. (1953): *Thorax*, **8**, 164.
Neville, W. E., and Munz, C. W. (1955): *Dis. Chest*, **27**, 447.
Overholt, R. H. (1943): *Dis. Chest*, **9**, 197.
Reiss, J. *et al.* (1952): *Dis. Chest*, **22**, 529.
Scatchard, G. N. (1944): *N.Y. St. J. Med.*, **44**, 617.
Victor, A. B. (1955): *Dis. Chest*, **27**, 389.

EXTRAPERIOSTEAL PLOMBAGE IN FAR ADVANCED PULMONARY TUBERCULOSIS

A REVIEW OF FIFTY CASES

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The increasing enthusiasm for resection in pulmonary tuberculosis has resulted in a steady decrease in the application of permanent surgical collapse procedures (Kelley and Pecora, 1952; Baffes *et al.*, 1954). Resection and collapse are, however, not necessarily competitive; each has its indications and should be resorted to accordingly. The most favourable results in excisional surgery are recorded in patients with limited, well stabilised, preferably unilateral disease.

This type of case has never presented a serious problem in the management of pulmonary tuberculosis. It is the patient with the far advanced, more diffuse, less stabilised disease who constitutes the real challenge. In such cases, prolonged conservative treatment—*e.g.*, antimicrobial therapy, temporary collapse procedures, etc.—have usually proved inadequate and pulmonary resection cannot be considered. For this group surgical collapse therapy may be the only chance. If one tends towards excision only one is likely to withhold surgical help from those patients who may need it most (O'Brien, 1952; Paine, 1955; O'Brien, Wilson, Armada and Vindzberg, 1953).

For many of these patients classical (multiple stage) thoracoplasty constitutes a major risk owing to the extensive decostalisation producing paradoxical chest wall movement and serious impairment of ventilatory function. Extraperiosteal plombage procedures with lucite spheres (Wilson, 1946; Woods, Walker and Schmidt, 1950) and polyethylene sponges (Bing, 1950; Engberg and Hansen, 1953) appear to be relatively simple and safe substitutes for classical thoracoplasty and avoid most of its shortcomings (Wilson *et al.*, 1955).

A review is here given of 50 patients who underwent 55 extraperiosteal plombage procedures during a three-year period ending June 1955. This group represents about 25 per cent. of all surgical interventions carried out for pulmonary tuberculosis in our services.

Our 50 patients include 36 males and 14 females aged between 18 and 59 years. All except one had bilateral disease, the majority were in a far advanced stage. Detailed information on each patient is furnished in the following table, the relevant data of which are commented upon.

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TABLE 1.—CLINICAL DATA ON 50 CASES OF EXTRAPERIOSTEAL PLOMBAGE

Name Age Sex	*Pulmonary tuberculosis*	*Preoperative status*	*Type of extraperiosteal plombage*	*Follow-up*
1. H.I. 30 M	Bilateral, advanced. Infiltration R.U.L. Infiltration with cavitation L.U.L.	Infiltration of R.U.L. regressed. Cavity 3×2 cm. L.U.L. Sputum positive	Left 5 ribs lucite balls with 2nd stage conversion. Thoracoplasty	23 months. At home. Working. Sputum negative.
2. K.S. 39	Bilateral, far advanced. Infiltration R.U.L. Infiltration with cavitations L.U.L.	Infiltration of R.U.L. regressed. Multiple cavities L.U.L. Sputum positive	Left 5 ribs lucite balls with 2nd stage conversion. Thoracoplasty	27 months. At home. Working. Sputum negative.
3. B.Y. 46 M	Bilateral, far advanced. Infiltration left lung. Infiltration with cavitations R.U.L. Endobronchial tuberculosis	Left lung infiltration regressed. Multiple cavities R.U.L. Sputum intermittently positive	Right 6 ribs lucite balls with 2nd stage conversion. Thoracoplasty	29 months. At home. Working. Sputum negative.
4. K.H. 22 M	Bilateral, advanced. Infiltration with cavitations both upper lobes. Endobronchial tuberculosis	Infiltration L.U.L. regressed. Multiple cavities R.U.L. Sputum positive	Right 5 ribs lucite balls with 2nd stage conversion. Thoracoplasty	Readmitted 5 months later. Spread in R.L.L. Cavity in sup. segm. R.L.L. Excision of R.U.L.+sup. segm. R.L.L. Improved. Sputum intermittently positive. Pneumoperitoneum.
5. S.M. 20 M	Bilateral, far advanced. Infiltration right lung. Infiltration with cavitations L.U.L.	Infiltration of right lung regressed. Multiple cavities L.U.L. Sputum positive	Left 6 ribs lucite balls with 2nd stage conversion. Thoracoplasty	21 months. At home. Working. Sputum negative.
6. S.A. 19 M	Bilateral, advanced. Infiltration with cavitations R.U.L. +sup. segm. R.L.L. Infiltration with cavitation left lung	Infiltration regressed in both lungs. Multiple cavities R.U.L. Cavity in apical segm. R.L.L. Sputum positive	Right 6 ribs lucite balls with 2nd stage conversion. Thoracoplasty	33 months. At home. Working. Sputum negative.
7. H.Y. 47 M	Bilateral, far advanced. Left lung infiltration with cavitation in lingula. Right lung infiltration with cavitation R.U.L. Right pachypleuritis. Endobronchial tuberculosis	Infiltration of left lung regressed. Multiple cavities R.U.L.	Right 6 ribs lucite balls with 2nd stage conversion. Thoracoplasty	Readmitted on year later. Sputum positive. Cavity in lingula reopened.

Endobronchial tuberculosis				
8. S.M. 22 M	Bilateral, advanced. Infiltration with cavitations both upper lobes	L.U.L. fibrocavitary pathology regressed. Tension cavity R.U.L. 3×3·5 cm. Sputum positive	Right 5 ribs lucite balls with 2nd stage conversion. Thoracoplasty	Readmitted 8 months later for excision. R.U. lobectomy. Improved. Sputum negative. Discharged.
9. M.S. 26 F	Bilateral, advanced. Infiltration with cavitations L.U.L. Fibrosis with cavitations R.U.L. of bronchiectatic type	Multiple cavities L.U.L. Sputum intermittently positive	Left 6 ribs lucite balls with 2nd stage conversion. Thoracoplasty	35 months. At home. Working. Sputum negative.
10. P.I. 40 M	Bilateral, advanced. Infiltration with cavitations both upper lobes, left side of bronchiectatic type	Infiltration L.U.L. regressed. Multiple cavities R.U.L. Sputum positive	Right 6 ribs lucite balls with 2nd stage conversion. Thoracoplasty	28 months. At home. Working. Sputum negative.
11. D.I. 22 M	Bilateral, far advanced. Infiltration L.L.L. Infiltration with cavitations R.U.L. (one tension cavity)	Infiltration L.L.L. regressed. Tension cavity R.U.L. 3×4 cm. Sputum positive	Right 7 ribs lucite balls with 2nd stage conversion. Thoracoplasty	35 months. At home. Working. Sputum negative.
12. K.M. 21 F.	Bilateral, advanced. Infiltration with cavitations R.U.L. +sup. segm. R.L.L. Healed cavity L.U.L. Endobronchial tuberculosis	Cavities R.U.L. (one of 2×2 cm.). Cavity apic segm. R.L.L. Sputum positive	Right 6 ribs lucite balls with 2nd stage conversion. Thoracoplasty	14 months. At home. Working. Sputum negative. 27 months. At home and working. Failed to report for further follow-up.
13. E.N. 53 M	Fibrocavitary disease of L.U.L.	Cavity 2×3 cm. L.U.L. Sputum positive	Left 6 ribs lucite balls with 2nd stage conversion. Thoracoplasty	20 months. At home. Working. Sputum negative. Shoulder improved.
14. I.I. 29 M	Bilateral, advanced. Infiltration L.U.L. Infiltration with cavitations R.U.L.	Infiltration L.U.L. regressed. Multiple cavities R.U.L. Sputum intermittently positive	Right 5 ribs lucite balls with 2nd stage conversion. Thoracoplasty	28 months. At home. Working. Sputum negative.
15. D.M. 22 F	Bilateral, advanced. Infiltration with cavitations both upper lobes	Infiltration R.U.L. regressed. Cavity L.U.L. 2×2 cm. Sputum positive	Left 5 ribs lucite balls with 2nd stage conversion. Thoracoplasty	37 months. At home. Reactivation R.U.L. Sputum positive.

TABLE I.—CLINICAL DATA ON 50 CASES OF EXTRAPERIOSTEAL PLOMBAGE (*continued*)

Name Age Sex	*Pulmonary tuberculosis*	*Preoperative status*	*Type of extraperiosteal plombage*	*Follow-up*
16. L.A. 30 M	Bilateral, far advanced. Infiltration with cavitations both upper lobes. Infiltration of entire right lung	Cavities of R.U.L. and infiltration of right lung regressed. Tension cavity L.U.L. 4×5 cm. Sputum positive	Left 6 ribs lucite balls with 2nd stage conversion. Thoracoplasty	33 months. At home. Working. Sputum negative.
17. S.S. 45 M	Bilateral, advanced. Fibrosis with cavitations R.U.L. Fibrosis L.U.L.	Cavities R.U.L. Sputum positive	Right 5 ribs lucite balls with 2nd stage conversion. Thoracoplasty	16 months. At home. Sputum negative.
18. S.S. 40	Bilateral, far advanced. Fibrosis with cavitations L.U.L. Infiltration R.U.L.	Infiltration R.U.L. repressed. Cavities L.U.L. Sputum intermittently positive	Left 5 ribs lucite balls with 2nd stage conversion. Thoracoplasty	37 months. At home. Sputum negative.
19. I.M. 33	Bilateral, far advanced. Infiltration both lungs. Cavitations both upper lobes	Infiltrations regressed. Cavities R.U.L. Sputum positive	Right 6 ribs lucite balls with 2nd stage conversion. Thoracoplasty	23 months. At home. Working. Sputum negative.
20. R.A. 25 M	Bilateral, far advanced. Fibrosis with cavitations R.U.L. Extensive infiltration both lungs	Infiltrations regressed. Cavities R.U.L.	Right 5 ribs lucite balls with 2nd stage conversion. Thoracoplasty	36 months. At home. Working. Sputum negative.
21. H.L. 30 F	Bilateral, far advanced. Multiple cavitations. R. upper lung field +apic segm. of R.L.L. Infiltration of entire left lung	Infiltration regressed. Cavities R.U.L. +sup. segm. R.L.L. Sputum positive	Right 6 ribs lucite balls with 2nd stage conversion. Thoracoplasty	Readmitted after 15 months. Excision of R.U.L. +apic segm. R.L.L. Improved. Sputum negative. Pyogenous infection of subscapular space requiring wound excision secondary suture. At home four years after operation. Sputum negative. Respiratory insufficiency.
22. N.I. 33 M	Bilateral, far advanced. Infiltration with cavitations R.U.L. Infiltration of entire left lung	Infiltrations regressed. Cavities R.U.L. Sputum positive	Right 6 ribs lucite balls	25 months. At home. Working. Sputum negative.

23. Z.M. 29 M	Bilateral, far advanced. Fibrosis right lung. Infiltration with cavitations L.U.L. Endobronchial tuberculosis	Infiltration regressed. Cavities L.U.L. Sputum intermittently positive	Left 6 ribs lucite balls	13 months. At home. Working. Sputum negative.
24. G.E. 27 M	Bilateral, advanced. Infiltration with cavitation L.U.L. R.U.L. bronchiectatic changes. Endobronchial tuberculosis	Cavities L.U.L. Sputum positive	Left 6 ribs lucite balls	9 months. Cavities closed. Sputum intermittently positive (culture). Renewed activity right side.
25. H.Y. 42 M	Bilateral, far advanced. Infiltration with cavitation L.U.L. Infiltration in both lower lobes. Endobronchial tuberculosis	Infiltrations regressed. Cavity L.U.L. 2×2 cm. Sputum positive	Left 6 ribs lucite balls	9 months. At home. Sputum negative.
26. B.R. 30 F	Bilateral, far advanced. Extensive infiltration both lungs. Cavity L.U.L. Pleuritis left	Infiltrations regressed. Tension cavity L.U.L. 4×5 cm. Sputum intermittently positive	Left 5 ribs lucite balls	9 months. At home. Sputum negative.
27. T.V. 33 F	Bilateral, far advanced. Extensive infiltration left lung. Infiltration with cavitation R.U.L. Endobronchial tuberculosis	Infiltrations regressed. Tension cavity R.U.L. 3×3 cm. Sputum positive	Right 6 ribs lucite balls	7 months. Spread in other part of the lung. Sputum positive. Antibiotic therapy.
28. A.Y. 45 M	Bilateral, far advanced. Infiltration both lungs. Cavitation R.U.L. Endobronchial tuberculosis	Infiltrations regressed. Cavity R.U.L. 1·5×3 cm. Sputum positive	Right 5 ribs lucite balls	6 months. At home. Working. Sputum negative. 8 months. Infiltration left lung. Sputum positive.
29. B.A. 34 M	Bilateral, advanced. Tension cavity L.U.L. State after right 7 rib thoracoplasty (1943) for tension cavity R.U.L.	Repeated hæmoptysis. Cavity L.U.L. 1×2 cm. Sputum negative	Left 5 ribs lucite balls	7 months. At home. Sputum negative.
30. B.F. 21 M	Bilateral, advanced. Infiltration with cavitations R.U.L. +L.L.L.	Infiltration regressed. Cavities R.U.L. Sputum positive	Right 5 ribs lucite balls	8 months. At home. Working. Sputum negative.

TABLE I.—CLINICAL DATA ON 50 CASES OF EXTRAPERIOSTEAL PLOMBAGE (*continued*)

Name *Age* *Sex*	*Pulmonary tuberculosis*	*Preoperative status*	*Type of extraperiosteal plombage*	*Follow-up*
31. R.M. 35 M	Bilateral, far advanced. Extensive infiltration both lungs. Cavities L.U.L. Pleuritis left	Infiltrations regressed. Large cavities L.U.L. Sputum positive	Left 6 ribs lucite balls	7 months. At home. Sputum negative.
32. S.Z. 43 M	Bilateral, far advanced. Cavitations R.U.L. of bronchiectatic type. Infiltration with cavitation L.U.L. Endobronchial tuberculosis	Infiltration regressed. Cavity L.U.L. 4×4 cm. Bronchiectasis R.U.L. Sputum positive	Left 6 ribs lucite balls Right 6 ribs lucite balls	6 months. Sputum intermittently positive. Intervention R. side considered.
33. F.E. 29 M	Bilateral, far advanced. Infiltration with cavitation L.U.L. (tension cavity 5×5·5). Infiltration right lung. Status post right. Extrapleural pneumothorax (1947) (abandoned)	Infiltrations regressed. Cavity L.U.L. 2×1·5 cm. Sputum positive	Left 6 ribs lucite balls	6 months. In sanatorium. Sputum negative.
34. F.A. 53 M	Bilateral, far advanced. Fibrosis of left lung. Cavitation R.U.L.	Cavity R.U.L. 2×3 cm. Sputum intermittently positive	Right 6 ribs lucite balls	10 months. In santorium. Sputum negative.
35. F.H. 47 M	Bilateral, far advanced. Infiltration with cavitations both upper lobes	Cavities R.U.L. regressed. Multiple cavities L.U.L. Sputum positive	Left 6 ribs lucite balls	7 months. Sputum intermittently positive. Cavitation in L.L.L. Subscapular effusion sterile requiring aspiration.
36. H.L. 18 F	Bilateral, far advanced. Infiltration with tension cavity R.U.L. Extensive infiltration left lung. Endobronchial tuberculosis	Infiltration left lung regressed. Tension cavity R.U.L. 4×5 cm. Sputum positive	Right 5 ribs Polystan	17 months. At home. Sputum negative. Readmitted 2 years later for reactivation of L.U.L. Cavity R.U.L. remained closed.
37. B.L. 40 F	Bilateral, far advanced. Infiltrations with cavitations both upper lobes. Endobronchial tuberculosis	Right pathology regressed. Cavities L.U.L. Sputum positive	Left 5 ribs Polystan	18 months. At home. Working. Sputum negative.

38. R.S. 26 F	Bilateral, advanced. Infiltration with cavitation L.U.L. (recidive after 11 y.). Infiltration R.U.L.	Infiltrations regressed. Cavity L.U.L. 2×2 cm. Sputum positive	Left 5 ribs Polystan	22 months. At home. Working. Sputum negative.
39. G.S. 35 F	Bilateral, far advanced. Destroyed right lung with giant cavitations. Extensive infiltration left lung. Endobronchial tuberculosis	Infiltration left lung regressed. Destroyed right lung. Sputum positive	Right 7 ribs Polystan	24 months. At home. Sputum negative.
40. Z.Y. 53 M	Bilateral, far advanced. Infiltration with cavitations R.U.L. Extensive infiltration left lung	Infiltration left lung regressed. Cavities R.U.L. Sputum positive	Right 6 ribs Polystan.	17 months. In sanatorium. Rest cavity under plombage suspected. Sputum positive. Antibiotic therapy. 22 months. Sputum converted.
41. B.A. 24 M	Bilateral, advanced. Fibrosis with cavitations R.U.L. Infiltration L.U.L.	Left infiltration regressed. Cavities R.U.L. Sputum positive	Right 5 ribs Polystan	3 years. Working. Sputum negative.
42. R.T. 25 M	Bilateral, advanced. Infiltration with cavitations R.U.L. Infiltration left lung	Infiltration left lung regressed. Cavities R.U.L. Sputum positive	Right 6 ribs Polystan	29 months. At home. Cavities closed. Sputum negative.
43. R.H. 34 M	Bilateral, far advanced. Infiltration with cavitations L.U.L. State after right 7 ribs thoracoplasty (1949)	Cavities L.U.L. Sputum positive	Left 4 ribs Polystan	13 months. At home. Working. Sputum negative.
44. F.K. 35 M	Bilateral, far advanced. Fibrosis of right lung. Fibrosis with cavitations L.U.L.	Cavities L.U.L. Cavity sup. segm. L.L.L. Sputum positive	Left 6 ribs Polystan	10 months. At home. Cavities closed. Sputum negative.

TABLE 1.—CLINICAL DATA ON 50 CASES OF EXTRAPERIOSTEAL PLOMBAGE (*continued*)

Name *Age* *Sex*	*Pulmonary tuberculosis*	*Preoperative status*	*Type of extraperiosteal plombage*	*Follow-up*
45. W.I. 52 M	Bilateral, far advanced. Infiltration R.U.L. Infiltration with cavitations L.U.L. Infiltration L.L.L.	Infiltrations regressed. Multiple cavities L.U.L. Sputum positive.	Left 5 ribs Polystan	12 months. Readmitted. Persistent lingular cavity. Sputum positive. Antibiotic therapy. Pneumoperitoneum. 16 months. At home. Lingula cavity disappearing. Culture intermittently positive.
46. S.M. 59 M	Bilateral, far advanced. Extensive infiltration both lungs. Cavitation R.U.L.	Infiltrations regressed. Cavity R.U.L. 3×2 cm. Sputum positive.	Right 5 ribs Polystan	13 months. At home. Working. Sputum negative.
47. R.M. 28 F	Bilateral, far advanced. Infiltration with cavitations L.U.L. Infiltration with cavitation R.U.L. Endobronchial tuberculosis	Infiltrations regressed. Cavities L.U.L. Cavity R.U.L. Sputum positive	Left 6 ribs Polystan Right 5 ribs Polystan	12 months. At home. Sputum negative.
48. L.R. 32 F	Bilateral, far advanced. Infiltration with cavitations both upper lobes	Infiltrations regressed. Cavities L.U.L. Cavities R.U.L. Sputum positive	Left 6 ribs Polystan Right 5 ribs Polystan	11 months. At home. Sputum intermittently positive (culture).
49. M.S. 35 F	Bilateral, far advanced. Infiltration with cavitations both upper lobes. Infiltration both lower lobes. Endobronchial tuberculosis	Infiltrations regressed. Cavities R.U.L. Cavities L.U.L. Soutum positive	Right 6 ribs Polystan Left 6 ribs Polystan	24 months. At home. Sputum intermittently positive (culture).
50. B.Y. 52 M	Bilateral, far advanced. Infiltration with cavitations both upper lobes	Infiltrations regressed. Cavities L.U.L. (one 3·5×2 cm.)	Left 5 ribs Polystan Right 5 ribs Polystan	14 months. Rest cavity R.U.L. Sputum positive (culture). Antibiotic therapy.

Comment

(1) Duration of disease: was between 1-14 years, averaging 5 years.

(2) Additional diseases: 17 patients had important additional disease unrelated to their pulmonary tuberculosis—*e.g.*, cardiovascular or metabolic disorders.

(3) Ventilatory function: was impaired in all except 3 patients; it was markedly reduced in 24.

(4) Previous therapy: all patients had been under prolonged conservative care, including bed rest, and antimicrobial therapy.

In the majority of them one or more of the following temporary collapse measures had been carried out with inadequate effect: intrapleural pneumothorax (sometimes bilateral), pneumoperitoneum, phrenic crush, external cavitary drainage (Monaldi).

(5) Sputum: in all 50 patients tubercle bacilli were found in the sputum prior to extraperiosteal plombage.

(6) Indication: in all patients extraperiosteal plombage was decided upon by a staff conference of physicians and surgeons. In none of these cases was excisional surgery even considered owing to the far advanced stage of the disease, complicating non-tuberculous pathology or impairment of ventilatory function. For the same reasons most of the patients were considered poor risks even for conventional thoracoplasty.

(7) Surgical procedure: 76 operative stages were performed on the 50 patients, all under general anaesthesia. In 45 cases the operation was unilateral, in 5 bilateral. The plombe was introduced extraperiosteally in all cases according to the technique described by Woods and co-workers (1950, 1953).

In 35 patients lucite spheres were used as plombage material; in 15 polyethylene sponges (" Polystan ") were employed.

In 21 of the 35 patients in whom lucite balls were inserted a second stage was performed about 3 months later when the spheres were removed and the denuded rib segments resected (" conversion thoracoplasty ").

In the remaining 14 patients, the lucite spheres were left as a permanent plombe, one was bilateral.

The same applies to the 15 cases where polystan plombage was employed: four were bilateral.

(8) Mortality, post-operative course, etc.: there was no mortality among the 50 patients.

The post-operative course was remarkably smooth in nearly all patients owing to the absence of paradoxical chest wall movement which made effective coughing and expectoration possible. There was only one case where post-operative atelectasis occurred. This was rapidly relieved by intratracheal suction. The wounds healed by primary intention in all cases, no wound disruption being observed. No infection of the extraperiosteal space or extrusion of the plombe occurred.

Partial intrapleural pneumothorax occurred in 3 cases owing to accidental tearing of the pleura during operation. One of these was associated with a hæmorrhagic effusion which had to be evacuated. In 2 cases moderate pleural effusion developed. This subsided without aspiration.

In 6 cases accumulation of serous fluid in the subscapular space was observed several weeks following operation; in 4 of them repeated aspirations had to be done. Bacteriological examination of the fluid was negative throughout.

Results

The post-operative follow-up period for all 50 patients varied from 6 months to 3 years.

Out of the 45 patients with unilateral plombage 36 became sputum negative within 6 months after operation; they showed marked clinical improvement, cavities no longer being visible on repeated X-ray examination, including tomography. In 4 of these 36 patients the sputum reverted to positive 9-24 months later owing to contralateral flare-up requiring readmission.

Of the 9 patients who failed to convert within 6 months 2 became negative 6-12 months later (No. 42, 46) under prolonged antimicrobial treatment. In 3 others after considerable general improvement and clearing of the contralateral process excision of the collapsed lobe was performed 8-15 months following plombage. In 2 of the resected cases the sputum converted readily (Nos. 8, 21); one has still intermittent positive cultures (No. 4). The remaining 4 patients remain sputum positive either because of persistent residual cavity under the plombe (No. 45) or because of spread in other parts of the lungs (Nos. 7, 27, 35).

All 5 patients with bilateral plombage are considerably improved clinically. Four are out of hospital and have resumed regular activity. Only 2 patients became sputum negative, the other 3 having intermittently positive cultures. One patient is still in hospital with a residual cavity under the plombe (No. 50).

Final Result in 50 Patients

Good (cavity closure, sputum negative, discharged)	38	=84%
Fair (suspected rest cavity, sputum culture intermittently positive, discharged)	4	
Bad (disease uncontrolled, sputum positive, in hospital)	8	=16%

Discussion

Notwithstanding the relatively short follow-up period the results can be regarded as encouraging if one considers that they have been obtained in patients who, owing to their far advanced disease and impaired pulmonary function, are rightfully labelled poor surgical risks. The majority of these cases have been repeatedly rejected by combined medical and surgical staff conferences as not amenable to surgical treatment. A salvage rate of 84 per cent. in such a group of cases with no operative death and minimal post-operative morbidity speaks clearly in favour of extraperiosteal plombage. We feel justified in including among the salvaged cases 4 who still have intermittently positive sputum cultures but are otherwise markedly improved and have resumed their regular occupation. We have also included 2 cases who required additional surgery because of residual cavities under the plombe and converted only after resection. Theoretically these 2 cases should be regarded as plombage failures; however plombage was instrumental in improving these patients' conditions to such an extent that excisional surgery—which was previously not

even considered—could be successfully performed. Even if one deducts these 6 cases from the overall salvage rate one would still arrive at a cavity closure and sputum conversion rate of 72 per cent. due to extraperiosteal plombage alone.

Similar results are reported by Woods and Buente (1953) who achieved primary conversion in 72 per cent. of their unilateral and 16 per cent. of their bilateral plombages; secondary conversion by additional surgical or antimicrobial treatment was obtained in 13 per cent. of the unilateral and 47 per cent. of the bilateral cases.

Joly and Villemin (1954) report on a series of 151 extraperiosteal plombages with a primary conversion rate of 79 per cent. This series includes a large number of good risk cases in whom selective resection or conventional thoracoplasty could have been employed.

Le Brigand (1954) reports good results in 60 per cent. of 60 extraperiosteal plombages.

Hansen (1954), using polystan for extraperiosteal plombage, reports his three years follow-up results in 100 cases: 63 per cent. sputum negative, 29 per cent. sputum positive, 8 per cent. dead. The majority of his patients were far advanced cases for whom other surgical procedures were not considered. This writer's material is very similar to ours.

Complications due to the presence of the plombage material such as effusion, infection with extrusion of the plombe, erosion of lung tissue or ribs and disruption of the wound have been reported by several authors (Engberg and Hansen, 1953; De Rougemont and Meyer, 1954; Hansen, 1954; Marmet and co-workers, 1954; Froehlich and Riniker, 1955; Lucas and Cleland, 1950; Davies *et al.*, 1951). However major complications appear to be rare and should not deter the surgeon from employing extraperiosteal plombage procedures where indicated. We have not observed significant complications in nearly 100 plombage operations performed up to date. In our first 21 cases of lucite ball plombage the material was removed at a second stage about 3 months after its insertion, since we were reluctant to leave the spheres permanently. The removed spheres as well as the small amount of fibrinous exudate found around them proved sterile in all cases and the extraperiosteal space was smooth and clean. The denuded rib segments were somewhat brittle but showed no signs of infection. On account of these findings which are in agreement with those of others (Woods and Buente, 1953; Wilson *et al.*, 1955), we abandon the second stage procedure and now leave the lucite spheres as a permanent plombe. Later removal of the lucite spheres which may become necessary if additional surgery (resection) has to be performed is technically easy, whereas the removal of a polystan sponge may be very difficult owing to the fact that it becomes adherent by ingrowing connective tissue. We therefore use polystan plombage only in those cases where further surgery does not bear consideration.

Ventilatory function studies have been done in most of our patients before and after extraperiosteal plombage. Only slight reduction of vital capacity occurred in these cases, whereas maximum breathing capacity even improved somewhat following operation (Milwidsky and Romanoff, 1955). These findings indicate that undesirable overcollapse of adequately functioning lung tissue can be avoided in extraperiosteal plombage, rendering it the permanent

collapse procedure of choice in patients who are poor surgical risks and whose ventilatory reserve is impaired.

Summary

A report is given on 50 patients with far advanced pulmonary tuberculosis on whom 55 extraperiosteal plombage procedures were performed. There was no mortality and only slight post-operative morbidity. The post-operative follow-up period ranged from 6 months to 3 years. The final results were good in 38, fair in 4 and bad in 8 cases; the overall salvage rate was 84 per cent.

Extraperiosteal plombage appears to be the permanent collapse procedure of choice in patients with far advanced cavitary tuberculosis in whom impaired ventilatory function and/or concomitant non-tuberculous disease preclude more extensive surgical measures.

REFERENCES

Baffes, T. G., Schlotterbeck, P., and DeCamp, P.T. (1954): *J. thorac. Surg.*, **27**, 349.
Bing, J. (1950): *Acta chir. Scandinav.*, **100**, 293.
Davies, H. Morreston, Temple, L. J., and Stathatos, C. (1951): *Thorax*, **6**, 209.
Engberg, H., and Hansen, J. L. (1953): *Acta tuberc. Scandinav.*, **128**, 45.
Froehlich, W., and Riniker, P. (1955): **12**, 336.
Hansen, J. L., and Engberg, H. (1953): *Acta chir. Scandinav.*, **105**, 335.
Hansen, J. L. (1954): *Le Poumon*, **10**, 207.
Joly, H., and Villemin, J. (1954): *Le Poumon*, **10**, 237.
Kelley, W. O., and Pecora, D. V. (1952): *J. thorac. Surg.*, **24**, 510.
Le Brigand, H. (1954): *Le Poumon*, **10**, 263.
Lucas, B. G. B., and Cleland, W. P. (1950): *Thorax*, **5**, 248.
Marmet, A., Jaubert de Beaujeu, M., Lévy, A., and Plane, J. (1954): *Le Poumon*, **10**, 223.
Milwidsky, H., and Romanoff, H. (1955): *Thorax*, **10**, 242.
O'Brien, E. J. (1952): *J. thorac. Surg.*, **23**, 340.
O'Brien, W. B., Wilson, N. J., Armada, O., and Vindzberg, W. V. (1953): *Amer. Rev. Tuberc.*, **68**, 874.
Paine, A. L. (1955): *J. thorac. Surg.*, **30**, 202.
Rougemont, J. De, and Meyer, L. (1954): *Le Poumon*, **10**, 203.
Wilson, D. A. (1946): *Surg. Clin. N. Amer.*, **26**, 1060.
Wilson, N. J., Armada, O., O'Brien, W. B., and Vindzberg, W. V. (1955): *Am. J. Surg.*, **89**, 663.
Woods, F. M., and Buente, L. (1953): *Amer. Rev. Tuberc.*, **68**, 902.
Woods, F. M., Walker, J. H., and Schmidt, J. (1950): *Dis. Chest*, **18**, 401.

TUBERCULOSIS AND LEUKÆMIA

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The association of tuberculosis, particularly of the disseminated type, with blood pictures suggesting leukæmia has long been known, and a large number of such cases has been published. The purpose in recording a further three cases is to draw attention to a clinical picture which is becoming neglected, and to report the effect of anti-tuberculous therapy.

Case 1. A housewife aged 41 was admitted to hospital on 15.2.52 on account of increasing lassitude, pallor, breathlessness on exercise, palpitations and anorexia. A sore throat, present for ten days, had responded partially to penicillin U. 500,000 b.d. Her temperature was 37·8° C., the throat was injected, and her mucous membranes were pale.

Investigations: Hb. 5·1 g.%, R.B.C.'s 1·3 m. per c.mm. (the red cells showed macrocytosis and anisocytosis), W.B.C.'s 1,700 per c.mm. (polymorphs 10%, eosinophils 2%, lymphocytes 68%, monocytes 20%). Platelets 200,000 per c.mm. (Lempert). Bone marrow: the majority of the cells present were lymphoblasts. X-ray chest: no abnormality seen. On 25.2.52 W.B.C.'s 1,000 per c.mm. (blast cells 6%, polymorphs 2%).

A diagnosis of acute lymphatic leukæmia having been made, she was transfused with four bottles of packed cells, and her hæmoglobin rose to 12·4 g. %. She was discharged on 12.3.52.

Up to June 1952 she required three blood tranfusions of two bottles of packed cells each. She was readmitted on 10.6.52 with swelling of the abdomen. The temperature was 37·6° C. and the distended abdomen contained a moderate amount of free fluid. The liver and spleen were enlarged 5 cm. below the respective costal margins, and a fixed hard mass 10 cm. ×7 cm. was palpable in the right iliac fossa. Small shotty lymph nodes were present in the neck. The stools were semi-solid but of normal colour. The Hb. was 10·2 g. %, W.B.C.'s 4,400 per c.mm. (polymorphs 17%, eosinophils 3%, lymphocytes 77%, monocytes 3%). A barium enema showed an irregular filling defect on the medial wall of the terminal ileum and the cæcum. The lesion in the right iliac fossa was considered to be lymphosarcomatous, but a course of deep X-ray therapy failed to reduce the size of the mass. She was discharged on 11.7.52.

She was readmitted on 30.7.52 with generalised miliary mottling on an X-ray of the chest. The peripheral leucocytes were essentially unchanged and the Hb. was 10·2 g. %. No tubercle bacilli were seen in six specimens of sputum, while culture for these organisms was negative. The C.S.F. was normal and no tubercle bacilli were recovered from the urine. At laparotomy on 29.8.52 (Mr. P. Hickenbotham) miliary tubercles were found studding the peritoneum, and hard lymph nodes extended from the right iliac fossa along the inferior vena cava. Microscopically the greater omentum showed appearances consistent with miliary tuberculosis, although no tubercle bacilli were seen.

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The diagnosis was now considered to be generalised tuberculosis with a lymphocytic leukæmoid reaction, and on 3.9.52 she commenced treatment with streptomycin 0·5 g. i.m. b.d. and PAS 5 g. by mouth q.d.s. Initially she improved, her fever settled, and the mass in the right iliac fossa decreased in size. At the end of October 1952 she started to deteriorate, again looking pale and fever recurring. On 1.11.52 the Hb. was 4·6 g. % and the W.B.C.'s 2,900 per c.mm. (polymorphs 4%, eosinophils 1%, lymphocytes 95%). The platelets were scanty. Her condition continued to worsen, she required increasingly frequent blood transfusions, developed purpura and became emaciated. She died on 15.1.53.

Post-mortem Summary

1. *Naked eye appearances:* Pallor of all organs, right-sided cerebral hæmorrhage, dark hæmorrhagic tissue in the right iliac fossa encircling the cæcum and part of the ascending colon and associated with multiple lymph node enlargement, liver 2,800 g., spleen 700 g.

2. *Histology:* Active miliary tuberculosis in both lungs, fibrosis with lymphocytic infiltration of the tissue around the cæcum with a tuberculous focus, caseous tuberculosis of an abdominal lymph node, large numbers of blast cells in the marrow, large numbers of blast cells in the spleen with some erythropoiesis, slight leukæmic infiltrations in the liver and kidneys.

Case 2. A shoe-clicker aged 55 was admitted to hospital on 6.5.53 complaining of increasing lassitude. For three days he had a deep vein thrombosis of the left calf. The temperature was 37·2° C. and the pulse 110/min. The left calf was tender and swollen with engorgement of the superficial veins.

Investigations: Hb. 10 g. %, W.B.C.'s 1,500 per c.mm. (polymorphs 6%, myelocytes 1%, lymphocytes 78%, monocytes 3%, probable myeloblasts 12%), platelets 200,000 per c.mm. (Lempert). Bone marrow: hyperplastic and consisting almost entirely of primitive cells considered to be myeloblasts. X-ray chest: a cavity in the left mid zone surrounded by shadowing extending into the upper zone. Six specimens of sputum: negative for T.B. on microscopy and culture.

The diagnosis was considered to be acute myeloid leukæmia, the lung lesions resulting from his agranulocytosis. Ethyl biscoumacetate (as an anti-coagulant) and chlortetracycline 250 mg. six-hourly by mouth were given for two weeks, and penicillin U. 500,000 i.m. b.d. for a further two weeks, but although the deep calf vein thrombosis resolved with only slight residual œdema, his general condition remained unchanged. On 13.6.53 an X-ray of the chest showed an increase in the size of the cavity with extension of the shadowing in the upper and middle zones. The Hb. had dropped to 6·4 g. % and the W.B.C.'s to 900 per c.mm. (polymorphs 20%, myeloblasts 4%, lymphocytes 74%, plasma cells 2%).

On the assumption that the lung lesions might be tuberculous, treatment with streptomycin 0·5 g. i.m. b.d. and isoniazid 50 mg. by mouth q.d.s. was commenced on 27.6.53 Within a few days the fever settled, the pulse rate returned to normal, and the general condition improved. On 15.9.53, when the anti-tuberculous therapy was stopped, the chest X-ray showed the shadowing in the left lung field to be resolving and the cavity to be smaller. The Hb. was 11·8 g. % and the W.B.C.'s 5,400 per c.mm. (polymorphs 7%, myeloblasts 44%). He was considered to have a myeloid leukæmoid reaction to his tuberculosis and was discharged on 19.9.53.

He was readmitted on 23.10.53 with cellulitis of the neck which slowly responded to chlortetracycline 250 mg. by mouth six-hourly administered for nine days. The Hb. was 8·9 g. % and the W.B.C.'s 18,600 per c.mm. (polymorphs 7%, promyeloblasts 14%, myeloblasts 40%, lymphocytes 29%). Bone marrow: hyperplastic with myeloblasts 83%. The chest radiograph remained unchanged. He was discharged on 2.11.53.

He was again admitted on 7.1.54 with another attack of cellulitis of the neck. The mouth was ulcerated, the liver was palpable 8 cm. below the right costal margin and the spleen 5 cm. below the left costal margin. The W.B.C.'s were 22,000 per c.mm. (polymorphs 2%, myeloblasts 68%). A chest X-ray now showed no evidence of cavitation and further reduction of the shadowing in the left lung field. Although the cellulitis partially responded to a further course of chlortetracycline, he slowly deteriorated and died on 26.1.54.

Post-mortem Summary

1. *Naked-eye appearances:* General wasting and pallor, excoriation of the lips and extensive ulceration of the buccal mucosa, partial obliteration of the pleural cavities, partial collapse of the left upper lobe, anthracosis and caseation in bronchial lymph nodes, liver 1,805 g., spleen 366 g. with obliteration of the follicles.

2. *Histology:* Caseating tuberculosis in the left upper lobe and some mediastinal lymph nodes, leukæmic infiltrations in the liver, spleen, lymph nodes and heart; replacement of the marrow by leukæmic tissue.

Case 3. A housewife aged 40 was seen in the outpatient department on 6.6.53, complaining of weakness, night sweats, loss of weight, and enlargement of the lymph nodes at the medial ends of both clavicles.

Investigations. X-ray chest: enlargement of the paratracheal and right hilar lymph nodes. Hb. 11·9 g. %, W.B.C.'s 3,000 per c.mm. (polymorphs 70%, lymphocytes 28%, monocytes 2%). Biopsy of a right supraclavicular lymph node showed caseous tuberculosis.

She was admitted to hospital on 11.8.53 with increasing lassitude, further loss of weight, shortage of breath and a purpuric rash over the lower abdomen and thighs. The temperature was 37° C. The mucous membranes were pale, the spleen tip just palpable, the cardiac dullness increased with an impalpable apex beat, the heart sounds were distant. The supraclavicular lymph nodes remained unchanged.

Investigations: Hb. 8 g. % (the red cells showed anisocytosis and macrocytosis with basophil stippling, a number of nucleated red cells were present), W.B.C.'s 5,600 per c.mm. (polymorphs 3%, myelocytes 3%, promyelocytes 48%, myeloblasts 36%, eosinophils 1%, lymphocytes 9%), platelets 233,000 per c.mm. (Lempert). Bone marrow: hyperplastic with 81% myeloblasts. X-ray chest: a large pericardial effusion was present, the lymph node enlargement previously noted was unchanged. E.C.G.: typical changes of pericarditis.

A diagnosis of a myeloid leukæmoid reaction to glandular and pericardial tuberculosis was made, and treatment with streptomycin 0·5 g. i.m. b.d. and isoniazid 50 mg. by mouth t.d.s. was commenced on 15.8.53. There was initial improvement with return of the temperature to normal and fading of the rash. The Hb. rose to 10·8 g. %, but the W.B.C.'s remained essentially unchanged. In the middle of September 1953 her fever recurred, she deteriorated, the purpura reappeared and the Hb. started to fall. Her condition was poor when she discharged herself on 25.11.53. At this time she had a constant pyrexia up

to 38° C., a purpuric rash covered her body, and leukæmic infiltrations were present in her lips. The liver was palpable 5 cm. below the right costal margin and the spleen 8 cm. below the left costal margin. The pericardial effusion appeared reduced in size and the supraclavicular nodes were less easily palpable. The Hb. was 8·3 g. % and the W.B.C.'s 4,700 per c.mm. (polymorphs 1%, metamyelocytes 2%, myelocytes 3%, promyelocytes 53%, myeloblasts 25%, lymphocytes 16%). The platelets numbered 19,000 per c.mm. (Lempert).

At home she received PAS 5 g. t.d.s. and isoniazid 100 mg. t.d.s., but continued to deteriorate. She was readmitted on 16.12.53 and died two hours after admission.

Post-mortem Summary

1. *Naked-eye appearances:* Petechiæ, ecchymoses and leukæmic infiltrations in the skin, pallor of all organs, congestion of the lungs, obliteration of the pericardium by organised blood clot, sero-sanguinous ascites, liver 2,300 g., spleen 415 g. with a uniform surface, bone marrow pale and gelatinous, lymph nodes firm and moderately enlarged, caseation of mediastinal lymph nodes.

2. *Histology:* Liver, spleen, lymph nodes, heart, kidneys and adrenals gross leukæmic infiltrations; marrow replaced by leukæmic tissue; mediastinal lymph nodes caseating tuberculosis.

Discussion

The association of active tuberculosis with blood pictures suggesting leukæmia was already recognised in the latter half of the nineteenth century, and a review of 45 such cases was published by Sussmann in 1903. The incidence is unknown, but the association seems uncommon, and Kirshbaum and Preuss (1943) were only able to find 16 quiescent cases of tuberculosis amongst their 123 cases of leukæmia. About 100 cases of active tuberculosis with blood pictures suggesting leukæmia have been published since 1920. Most of these have suffered from miliary tuberculosis, and reports of more localised disease have been correspondingly less frequent. At post-mortem varying degrees of leukæmic infiltration have been found, and it is possible to recognise three groups:

I. Cases with marked leukæmic infiltrations indicative of true leukæmia.
II. Cases with less marked or slight leukæmic infiltrations in which the diagnosis of leukæmia has been considered doubtful.
III. Cases without leukæmic infiltrations considered to have shown leukæmoid reactions to severe tuberculosis.

Group I. In this group there could be no doubt regarding the diagnosis of leukæmia, although the exact relationship of the leukæmia to the tuberculous process has often not been clear. In some cases extension of a tuberculous focus has been observed during the development of a leukæmia, and this has frequently taken the form of an acute miliary dissemination (Mills and Townsend, 1937; Farber and Bylebyl, 1942; Gardner and Mettier, 1949; Rothstein and Jarrold, 1954; Sachs, 1954). This miliary process was often characterised histologically by marked necrosis, poor cellular reaction and abundant tubercle bacilli. Similar forms of miliary tuberculosis have been reported in other cases of leukæmia, suggesting that in these cases also the leukæmia was responsible for the tuberculous spread (Hemmerling and Schleusing, 1927;

Boattini, 1931; Marzullo and de Veer, 1931; Jaffé, 1933; Fischer, 1935; Massias, 1948). Any debilitating disease may cause deterioration in pre-existing tuberculosis, but in leukæmia the reduced phagocytic activity of immature leucocytes (Hertzog, 1938) must be regarded as an additional factor. Only a few cases have been reported in which the leukæmia appears to have exerted little influence on an accompanying tuberculosis (Jaffé, 1933; Ryan and Medlar, 1937; Hernandez and Smirnoff, 1946).

Group II. The cases in this group all suffered from generalised tuberculosis (Lenhartz, 1932; Mattisseck, 1941; Desclin and Gepts, 1950; Betz and Liégeois, 1953; Zylberzac *et al.*, 1953). They resembled the cases of true leukæmia with miliary tuberculosis, except that the leukæmic infiltrations were less severe. Death appears to have been the result of their tuberculosis, and had they survived longer it seems likely that the leukæmic infiltrations would have been more marked.

Group III. The cases in this group all died with acute, and nearly always with generalised, tuberculosis (Mills and Townsend, 1937; Leibowitz, 1938; Sterner, 1939; Stöger, 1940; Zylberzac *et al.*, 1953). In the absence of leukæmic infiltrations such cases have been considered to be examples of leukæmoid reactions to severe infection (Thompson, 1931; Leitner, 1949), but early leukæmia may be the basis of these leukæmoid blood pictures. Not all leukæmoid reactions to tuberculosis have been similar in type, and although most cases have shown granulocytic blood pictures, lymphatic and monocytic hyperplasia have also been reported (Gibson, 1946; Gardner and Mettier, 1949). Occasionally leukæmoid reactions have been observed for more than one year, although the associated miliary tuberculosis was not recognised during life (Krasso and Nothnagel, 1925; Jaffé, 1933; Heinle and Weir, 1944). In the case of Heinle and Weir (1944) a granulocytic picture was present for five years, and it seems that recent extension of a fibro-caseous pulmonary tuberculosis was responsible for the miliary spread. No clear-cut division can be demonstrated between cases with relatively slight and those without leukæmic infiltrations, and at times the marrow has been thought to show leukæmia, although other leukæmic infiltrations were absent (Leitner, 1949; Staffurth and Spencer, 1950; Zylberzac *et al.*, 1953).

It is suggested that all cases in group II and many in group III suffered from early leukæmia and that they died from acute tuberculosis at a relatively early stage of their leukæmia. Their tuberculosis, as in cases with marked leukæmic infiltrations, was frequently characterised by severe necrosis, poor cellular reaction, and abundant tubercle bacilli. This type of disease has been reported in association with other blood abnormalities, including leucopenia, pancytopenia, myelosclerosis and polycythæmia (Crail *et al.*, 1948; Guild and Robson, 1950; Ball *et al.*, 1951; Medd and Hayhoe, 1955). Only one case of miliary tuberculosis in association with a blood dyscrasia has been reported to have survived. He suffered from leucopenia which was unaffected by fifteen months' treatment with streptomycin and isoniazid (Medd and Hayhoe, 1955). Medd and Hayhoe have suggested that tuberculosis may cause hæmatological abnormalities, but it seems more probable that primary blood disease can be responsible for the activation of a tuberculous focus.

Treatment. Reports of specific anti-tuberculous therapy in cases of tuber-

culosis with blood pictures suggesting leukæmia have been few. Some improvement was obtained by Rothstein and Jarrold (1954) in a case of myelogenous leukæmia, by Sachs (1954) in a case of lymphatic leukæmia, and by Zylberzac *et al.* (1953) in two patients with granulocytic blood pictures, but all four cases died with active miliary tuberculosis.

Many cases of true leukæmia have received radiotherapy, the response being more satisfactory in the chronic type of case (Thompson, 1931; Rothstein and Jarrold, 1954). In cases without leukæmic infiltrations a reduction in the number of circulating leucocytes was often obtained without corresponding clinical improvement (Thompson, 1931; Heinle and Weir, 1944; Spier and Cluff, 1948). Chevallier *et al.* (1954) treated two cases without leukæmic infiltration with ACTH, but its effect was difficult to assess.

The Present Cases. These include one man and two women whose ages ranged from 40 to 55. While most previous cases have been middle-aged, they have been predominantly male. Cases 1 and 2 presented with leukæmia, and their tuberculosis was not suspected for some time. The tuberculosis in case 1 was first considered after an X-ray of the chest and confirmed at laparotomy, and in case 2 after the lung cavity had failed to respond to chlortetracycline and penicillin. Case 3 presented with tuberculous glands in the neck, and her leukæmia only became apparent some weeks later. In many cases in which the tuberculosis was not suspected during life, lesions which should have been visible on an X-ray of the chest were present at post-mortem, and such an investigation appears, therefore, desirable in all patients with leukæmoid blood pictures. A liver biopsy would have revealed tuberculosis in the remaining cases, but as this test may be considered to involve undue risk, it may occasionally prove necessary to administer specific anti-tuberculous therapy to cases with leukæmoid blood pictures in the absence of a firm diagnosis.

All three cases were thought to have leukæmoid reactions to their tuberculosis, and their initial improvement on streptomycin and PAS or isoniazid was considered to favour this diagnosis. In case 1, an example of group II, relatively slight lymphatic leukæmic infiltrations were found at post-mortem. She was treated with streptomycin and PAS, but the persisting active miliary tuberculosis was thought to be the main cause of her death. The patient might have survived longer with additional treatment with isoniazid, but then the leukæmic infiltrations would probably have been more pronounced. The relationship of the tuberculosis to the leukæmia in this case was not entirely clear, but it seems that leukæmia, and possibly the radiotherapy, were responsible for the spread of the tuberculosis. Cases 2 and 3, both examples of group I, were of particular interest in that considerable regression of the tuberculosis was obtained in the presence of granulocytic leukæmia. This degree of improvement of tuberculous lesions in the presence of leukæmia has not been reported previously. Although it is probably related to the absence of miliary spread in both cases, the shrinking of the lymph nodes in case 2 and the closure of the cavity in case 3 in response to streptomycin and isoniazid were pronounced. As both cases were thought to have leukæmoid reactions, anti-leukæmic drugs were not administered.

Summary and Conclusions

1. Three cases are described in which leukæmoid blood pictures were associated with active tuberculosis.

2. All three cases were considered to have leukæmia, and it is suggested that many cases thought to show leukæmoid reactions to tuberculosis actually suffered from leukæmia.

3. As the diagnosis of tuberculosis in cases with leukæmoid blood pictures has frequently been delayed, an X-ray of the chest should be considered an essential investigation, and occasionally empirical treatment with streptomycin and isoniazid may be indicated.

4. It is shown that a satisfactory response to anti-tuberculous therapy can be obtained in the presence of leukæmia.

5. Anti-leukæmic treatment appears indicated when regression of a tuberculous process is unaccompanied by a correspondingly clinical and hæmatological improvement.

My thanks are due to Dr. J. P. W. Jamie (case 1) and Dr. S. E. Tanner (cases 2 and 3) for permitting me to describe cases under their care, to Dr. E. M. Ward and Dr. E. M. Stirk for the hæmatological and post-mortem reports, and to Dr. E. K. Blackburn for his helpful advice in the preparation of this paper.

REFERENCES

Ball, K., Joules, H., and Pagel, W. (1951): *Brit. Med. J.*, **2**, 869.
Betz, H., and Liégeois, A. (1953): *Acta clin. belg.*, **8**, 219.
Boattini, G. (1931): *Hæmatologica*, **12**, 423.
Chevallier, P., Bernard, J. Bilski-Pasquier, G., and Christol, D. (1954): *Semaine Hôp. Paris*, **30**, 765.
Crail, H. W., Alt, H. L., and Nadler, W. H. (1948): *Blood*, **3**, 1426.
Desclin, L., and Gepts, W. (1950): *Acta clin. belg.*, **5**, 197.
Farber, J. E., and Bylebyl, H. (1942): *Amer. J. Clin. Path.*, **12**, 253.
Fischer, W. (1935): *Beitr. Klin. Tuberk.*, **87**, 334.
Gardner, F. H., and Mettier, S. R. (1949): *Blood*, **4**, 767.
Gibson, A. (1946): *J. Path. Bact.*, **58**, 469.
Guild, A. A., and Robson, H. N. (1950): *Edin. med. J.*, **57**, 145.
Heinle, R. W., and Weir, D. R. (1944): *Amer. J. med. Sc.*, **207**, 450.
Hemmerling, H., and Schleusing, H. (1927): *Deutsches Arch. klin. Med.*, **157**, 309.
Hernandez, I. M., and Smirnoff, I. (1946): *Asso. med. argent.*, **60**, 677.
Hertzog, A. J. (1938): *Amer. J. Path.*, **14**, 595.
Jaffé, R. H. (1933): *Amer. Rev. Tuberc.*, **27**, 32.
Kirshbaum, J. D., and Preuss, F. S. (1943): *Arch. Int. Med.*, **71**, 777.
Krasso, H., and Nothnagel, H. (1925): *Wien. Arch. inn. Med.*, **11**, 507.
Leibowitz, S. (1938): *Arch. Path.*, **25**, 365.
Leitner, S. J. (1949): "Bone Marrow Biopsy." London: J. and A. Churchill.
Lenhartz, H. (1932): *Beitr. Klin. Tuberk.*, **79**, 501.
Marzullo, E. R., and de Veer, J. A. (1931): *Amer. J. med. Sc.*, **182**, 372.
Massias, C. (1948): *Sang.*, **19**, 121.
Mattisseck, H. (1941): *Arch. path. Anat.*, **308**, 783.
Medd, W. E., and Hayhoz, F. G. J. (1955): *Quart. J. Med.*, **24**, 351.
Mills, E. S., and Townsend, E. R. (1937): *Canad. med. Ass. J.*, **37**, 56.
Rothstein, E., and Jarrold, T. (1954): *Amer. Rev. Tuberc.*, **70**, 509.
Ryan, W. J., and Medlar, E. M. (1937): *Amer. Rev. Tuberc.*, **36**, 212.
Sachs, V. (1954): *Ärztl. Wchnschr.*, **9**, 481.
Spier, J., and Cluff, L. E. (1948): *M. Ann. Distr. Columbia*, **17**, 98.
Staffurth, J. S., and Spencer, H. (1950): *Blood*, **5**, 1161.
Sterner, L. G. (1939): *Nord. Med.*, **2**, 1457.
Stöger, R. (1940): *Wien. klin. Wchnschr.*, **53**, 419.
Sussmann, W. J. (1903): *Practioner*, **71**, 536.
Thompson, W. P. (1931): *Amer. J. med. Sc.*, **182**, 334.
Zylberzac, S., Denolin-Reubens, R., and Lambert, P. P. (1953): *Acta clin. belg.*, **8**, 227.

TUBERCULOSIS AND THE PUERPERIUM

A TRIAL OF CHEMOTHERAPY AND ŒSTROGENS

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Introduction

Studies on tuberculous women in the puerperium still show disturbing relapse rates, although medical opinion varies on this subject. In this unit intensive chemotherapy and, more recently, the addition of œstrogen therapy in the puerperium have shown very encouraging results.

For the last decade pregnancy in the tuberculous has been regarded as an incident carrying no increased risk. The views of such authors as Cohen (1946), Stewart and Simmonds (1947), and Midgley Turner (1950), that childbearing has no influence on the progress of active and quiescent cases, are based on long-term follow-up studies.

In spite of this the first trimester and the puerperium are still quoted as times of peculiar hazard for the tuberculous. Beven (1952) produced a very detailed paper confirming the grave influence of the puerperium; among his active cases there was a relapse rate of 43 per cent. during the first two months after delivery. Cromie (1954), in a report from Northern Ireland, found that half his patients with active disease deteriorated either during pregnancy or in the subsquent six months. Beven's paper came from the unit at Grove Park Hospital which deals entirely with antenatal and post-natal patients with pulmonary tuberculosis.

This report comes from the same unit, and we have tried to assess the present risks and the results of current treatment. Our attention has been directed particularly to the possible influence of endocrine factors on the tuberculous process. Browne *et al.* (1939) estimated the varying blood levels of œstrogen and chorionic gonadotropin during pregnancy and the puerperium. A notable rise of gonadotropin occurs in early pregnancy and is followed by a fall to near normal levels by the fifth month. The œstrogen level rises steadily from the fourth month, and falls abruptly at parturition. Lurie *et al.* (1949) found that in mature rabbits œstrogens retarded the tuberculous process at the site of inoculation into the skin, while gonadotropins increased it: the œstrogens appeared to have a protective effect. It has been suggested that the deterioration in early pregnancy may be related to the high level of gonadotropin in the blood, and that the puerperal deterioration may be partly attributed to the fall in œstrogens at parturition.

Beven's paper was written in the early years of chemotherapy when the drugs were not so freely used as they are to-day. Few of his patients were receiving chemotherapy at the time of delivery nor in the puerperium. It was

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decided, therefore, to attempt to assess and compare the effects of two régimes of treatment:

I. Chemotherapy before and after delivery.
II. Chemotherapy before delivery, and chemotherapy and œstrin after.

Material

The total hospital material comprises 130 cases, treated between June 1953 and December 1955. There were 68 primigravida and 62 multigravida. Fifty-seven patients were under 26 years, and 73 over that age. One hundred and four patients had active disease and a more detailed classification of them is given below:

Tuberculosis diagnosed during this pregnancy	57
Chronic active tuberculosis	27
Tuberculosis reactivated during this pregnancy	20

Of the newly diagnosed cases 22 (38 per cent.) were found on routine antenatal X-ray. The large majority of the new cases were diagnosed in the first six months of pregnancy. The significance of the first trimester in the reactivation of tubercle is shown by the fact that, of the 20 patients who were admitted because of reactivation of their lesions, this had occurred in the first trimester in 10. There were also 26 patients whose disease was considered by us to be quiescent. It should be noted, however, that all patients entering this unit are admitted at least six weeks before the expected date of delivery and remain in for at least six weeks afterwards, so that even quiescent cases may be expected to have some disquieting feature warranting this period of care.

For our investigation we took two series of active cases, the first consisting of 46 patients treated between June 1953 and September 1954: the second comprising 58 patients treated since October 1954. The two series are comparable as regards age and parity, and their Ministry of Health classification is shown in Table I, and it may be well at this point to compare our type of case with that in Beven's paper.

Table I.—Classification of Disease

	A_1	A_2	B_1	B_2	B_3
Series I	2	15	0	19	10
Series II	3	14	1	34	6
Total	5	29	1	53	16
Beven (1952)	12	20	17	60	18

As might be expected, Beven's cases collected five years ago were more advanced than ours. However, our own series are reasonably comparable with each other. There is also close similarity between the two series in the type of disease—*e.g.*, newly diagnosed, chronic active, or reactivated.

Treatment

The patients in both series were given a minimum period of one month of a suitable combination of antituberculous drugs—*e.g.*, streptomycin, PAS, or INAH before delivery; these drugs were continued after delivery for a minimum of six weeks. (In most cases much longer courses of drugs were used both before and after the confinement.) In addition the cases in Series II had a minimum of six weeks of an œstrin preparation, either Stilbœstrol 5 mg. t.d.s., or ethinyl œstradiol 0·2 mg. t.d.s. from the day of the confinement. The full course of œstrin therapy lasted for three months, and the majority of the patients had this. (On this unit previously an œstrin preparation was given routinely for ten days post-partum to suppress lactation.)

Each patient was X-rayed monthly and had tomograms on admission and six weeks post-partum. Three sputum cultures were set up on admission, and repeated at intervals. Six consecutive sputum cultures were set up post-partum, and three direct examinations made at six weeks after delivery.

Results

Active Cases

The relapses in the first two months of the puerperium in our two series and in Beven's cases are given in Table 2.

Table 2.—Puerperal Relapse Rates on Different Treatment Régimes

	Beven	*Series I*	*Series II*
No. of cases	114	46	58
No. relapsing within two months of delivery	49	10	4
% relapse	43%	21%	7%

Details regarding the 14 relapses in the present trial are given in Tables 3 and 4.

Table 3.—Type of Relapse

Spread of disease	9
Cavity enlargement	3
Positive sputum culture	1
Breakdown of solid focus	1

Table 4.—Time of Relapse Post-partum

Within 2 weeks	3
„ 4 „	4
„ 6 „	5
„ 8 „	2

Relapses occurred in 5 primigravida and 9 multigravida. There were 8 in 46 patients under 26 years, and 6 in 58 patients over 26 years. The younger patient therefore seems to run a slightly greater risk, as one might expect with tuberculosis in women. Their Ministry of Health classification was: 3 A_2 cases, 10 B_2 cases, and 1 B_3 case.

Relapses occurred in both the newly diagnosed cases (8 in 57 cases) and in chronic active cases (5 in 27). There was only one relapse among the 20 patients who reactivated during pregnancy; this would seem to be related to the fact that the disease was probably treated and under control again before delivery. On the whole, however, more prolonged treatment before delivery did not appear to be a safeguard. Of 48 patients treated for more than three months before delivery, 6 relapsed: of 32 treated for two months, 3 relapsed: and of 50 treated for one month, 5 relapsed.

It should be mentioned that all the relapses we observed were minimal and the final outcome was probably not affected by them. Possibly the fact that the patients were on treatment minimised such deterioration as occurred.

In addition to treatment with chemotherapy, a pneumoperitoneum was induced in 4 cases. Fifteen patients proceeded to excisional surgery, and 7 had thoracoplasties. In no case was it found necessary to operate during pregnancy, and surgery was carried out at a suitable time after the second month post-partum.

Quiescent Cases

There were in addition 26 patients with quiescent disease, who were treated with the same régime as Series II—that is, with antenatal and post-natal drugs and œstrin. Among this group there was only one relapse.

As a control group for comparison with our hospital figures, we studied a series of 100 tuberculous women attending Lewisham Chest Clinic, and delivered between 1950 and 1955. Their disease was considered stable, and they received no special care or treatment over their confinements, beyond the fact that many did not breast feed. Nine of these patients deteriorated within two months of delivery, and details in each year are given in Table 5.

TABLE 5.—RELAPSES IN QUIESCENT CLINIC CASES

Year	*No. of cases*	*Relapses in puerperium*
1950	7	0
1951	8	2
1952	16	2
1953	18	0
1954	20	1
1955	29	4

In such a study as this, it is desirable to have figures of the average relapse rates for tubercle treated with modern antibiotic and chemotherapeutic drugs. Such figures are difficult to obtain and it is for this reason that we have included for comparison a short series of non-pregnant women in the same age group, treated at the same hospital, and observed by one of us (B.T.). All were active cases, and various régimes of treatment were used. The results in Table 6 show relapses that occurred in the second to the fourth months of hospital treatment, this being a period comparable in time with the first two months of the puerperium in our cases. There were 50 cases, with 2 relapses, giving a relapse rate of 4 per cent.

TABLE 6.—RELAPSES IN NON-PREGNANT ACTIVE CASES

Deterioration on bed rest only	1
„ „ single chemotherapy	1
„ „ combined chemotherapy	0
TOTAL RELAPSES	2
Relapse rate	4%

Discussion

The problem of a peculiar risk for the tuberculous during pregnancy is still unsolved. When approaching this subject on the basis of our results, there are two significant facts to bear in mind. Firstly, these relapses are occurring within the very short period of two months, and secondly, all the patients were on active treatment at the time.

Papers such as those of Beven and Cromie suggest that there is a definite danger, whereas those of Stewart and Simmonds maintain that in the long run there is no significant effect. Possibly data obtained from in-patients where observation is closer will give higher relapse rates. It may be that discrepancies between the reports arise because the first two authors collected their data shortly after delivery, whereas Stewart and Simmonds' follow-up was carried out eighteen months later. This would suggest that the tendency to deteriorate may be self-limiting. This further report from the Grove Park Unit supports the view that the puerperium is an unfavourable period.

Puerperal relapses may be due to one (or both) of two main factors, mechanical and constitutional, including hormonal. Those occurring immediately after delivery (within hours or days) may have a mechanical basis, and such instances might be prevented by a large pneumoperitoneum.

Earlier diagnosis and more effective treatment have wholly altered the prognosis in tuberculosis; hence comparison with previous findings are unreliable. The figures set out below can only be used to show current results.

For active cases Beven found a puerperal relapse rate of 43 per cent., on Sanatorium régime. Our relapse rate was 22 per cent. on chemotherapy (Series I), and 7 per cent with the addition of œstrin in the puerperium (Series II).

This latest figure is so low, and the character of the relapses so minor, that we have not considered termination justifiable on the grounds of pulmonary tuberculosis in any of our cases.

The difference between the results of Series I and Series II is considerable and would strongly suggest that the administration of high doses of œstrin in the puerperium has a marked effect in reducing the number of relapses.

As regards the quiescent cases, the clinic figure of a 9 per cent. relapse rate compares unfavourably with that for quiescent cases treated with drugs and œstrin (one relapse in 26 cases), especially when bearing in mind that the quiescent cases would not have been in our unit unless there was some cause for anxiety. The findings in this unit suggest that, as with the active cases, so with the quiescent cases, the best results may be achieved with antenatal and post-natal drugs and œstrin.

Apart from the material used for this report there have been a few quiescent cases on the unit treated by variations of our standard régime; they are included in Table 7.

TABLE 7.—RELAPSES IN QUIESCENT CASES

Type of treatment	*No. of cases*	*Relapses*
No active treatment (clinic cases)	100	9
No active treatment (hospital cases)	8	1
Post-natal œstrin only	5	3
Post-natal chemotherapy and œstrin	6	1
Ante-natal and post-natal chemotherapy and post-natal œstrin	26	1

There seems little justification for the use of œstrin alone in the puerperium.

There does not appear to be any risk attached to treating the pregnant woman with chemotherapy throughout long periods of her pregnancy, and all the infants have appeared unaffected. As regards the use of œstrin, this very large dose is well tolerated by the puerperal woman. One patient in her forties developed menorrhagia after withdrawal of œstrin, and we would perhaps avoid œstrin again in elderly gravida.

Summary

We have treated a group of pregnant tuberculous women with chemotherapy and œstrogens. A régime of antenatal and post-natal chemotherapy, and œstrogens for a minimum of six weeks post-partum, has given a very low relapse rate in the puerperium.

We should particularly like to thank our Consultant Obstetrician and Gynaecologist, Mrs. J. Karnicki, whose advice and encouragement made this study possible.

It is also a pleasure to thank Miss Eunice Maddock, the unit Sister, for all her help.

REFERENCES

BEVEN, G. (1952): *Tubercle*, **32**, 1, 13.
BROWNE, J. S. L. *et al.* (1939): *Amer. J. Obst. Gynæ.*, **38**, 927.
COHEN, R. C. (1946): *Brit. J. Tuber. Dis. Chest*, **40**, 10.
CROMIE, J. B. (1954): *Brit. J. Tuberc. Dis Chest*, **48**, 97.
LURIE, M. B. *et al.* (1949): *Amer. J. Tuberc.*, **59**, 169, 186.
STEWART, C. J. and SIMMONDS, F. A. H. (1947): *Brit. med. J.*, **2**, 726.
TURNER, H. M. (1950): *Lancet*, **1**, 697.

PULMONARY TUBERCULOSIS AFTER THE AGE OF FIFTY

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Among the causes of illness of the increasing elderly male population in this country pulmonary tuberculosis plays a prominent part. This is of importance because the disease can be controlled by modern chemotherapy, as will be seen in this paper, and, therefore, some of these older patients may be enabled to continue to play some part in productive work. It is of further importance because the disease in this group of people forms a pool of infection which is a hazard to others.

The mortality rate for pulmonary tuberculosis and the number of notifications is declining in the population as a whole, but in older males, especially those over 65, they still remain high, whereas in older females this mortality rate is declining. (Ministry of Health Rep. 1955. Heaf, 1955.)

Material

In this study 106 patients over the age of 50 years with pulmonary tuberculosis and a positive sputum have been investigated while under the care of St. Thomas's Hospital (North Lambeth Chest Clinic) during the last six years.

Table I.—Radiological Extent of Disease and Cavitation by Sex and Age

	No. of Males					*No. of Females*				
Age	*Class I*	*Cl. II*	*Cl. III*	*Cav.*	*Total*	*Cl. I*	*Cl. II*	*Cl. III*	*Cav.*	*Total*
50-54	5	18	5	21	28	3	4	1	5	8
55-64	7	19	14	21	40	1	3	4	5	8
65-74	2	8	8	4	18	1	2	1	3	4
Total	14	45	27	46	86	5	9	6	13	20

Class I.—Not more than 1 zone in 1 lung involved.
Class II.—Unilateral or bilateral disease involving 2 or 3 zones.
Class III.—Bilateral disease affecting 4 or more zones.

(Foster-Carter *et al.*, 1952.)

Table I summarises the age and sex distribution of the patients in this survey, and the radiological extent of the disease and frequency of cavitation, and Tables II, III and IV show their distribution in social classes, their working and living conditions. Table II shows that the majority of males and females fall into classes IV and V, skilled and unskilled manual workers. Women who were not working were classified according to their husbands' occupations. The working conditions of the males (Tables III) show clearly the long hours most of the patients worked before diagnosis. Five female patients were gain-

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fully employed in addition to their household duties; this was indoors, day work, and not exceeding 45 hours per week. The household conditions are summarised in Table IV. The majority were living *en famille*, while a proportion were single, separated or bereaved. Rehousing was recommended in 34 (32 per cent.). Recent anxieties due to domestic stresses—*e.g.*, separation, divorce, unhappy marriages, recent illness or death of close relative—had occurred in at least 44 (41·5 per cent.).

TABLE II.—NUMBER OF TUBERCULOUS PATIENTS IN SOCIAL CLASSES

Number of Patients

Social Classes	*Male*	*Female*	*Total*
I.—Professional	0	2	2
II.—Intermediate	1	0	1
III.—Skilled non-manual	19	0	19
IV.—Skilled manual	33	7	40
V.—Unskilled	33	11	44

TABLE III.—WORKING CONDITIONS OF MALES PRIOR TO THE DIAGNOSIS

Working Conditions (Males)

	Shift work	Night work (indoors)	Night work (outdoors)	Day work (outdoors)	Day work (indoors)	40 hrs. or less per week (including overtime)	41-50 "	51-60 "	61-70 "	71-80 "	Total at work	Total retired
No. of patients	9	8	5	24	43	3	33	32	12	3	83	3

TABLE IV.—LIVING CONDITIONS (MALES AND FEMALES)

	Housing Situation					Domestic Features						
	Living "en famille"	Alone in own home	In lodgings	In hostels	Unsatisfactory housing; rehousing recommended	Married: spouse well	Married: spouse invalid	Widowed	Single	Married unhappily	Separated or divorced	Worry about recent illness or death of close relative
No. of males	63	5	15	2	30	46	8	5	16	9	11	19
No. of females	12	6	0	2	4	10	2	3	5	1	0	8
TOTAL	75	11	15	4	34	56	10	8	21	10	11	27

Clinical Features

For the purposes of this study it was found of interest to compare the clinical presentation of the patients in this series with a comparable series under 50 years. Table V depicts the differences in clinical presentation.

Patients over 50 revealed greater evidence of cough and breathlessness and, to some extent, more frequent non-respiratory symptoms than in those under 50. Other chest symptoms such as pain and hæmoptysis did not differ significantly in the two groups. Those over 50 with symptoms were referred by their doctors; all these had a cough. Of 49 who had an acute respiratory illness, 24 were previously well, 15 had a progressive cough and 10 a cough and non-respiratory symptoms. Nineteen patients had progressive respiratory symptoms and 30 exhibited non-respiratory symptoms as well as progressive respiratory symptoms.

In the majority of those over 50 the respiratory and non-respiratory symptoms of gradual onset varied from 6 months to 2 years. Ten had a cough for 3-10 years and 15 had a cough for "many" years. In the under 50 group the average duration of non-respiratory symptoms was 4 months and of respiratory symptoms 3 months.

Table V.—Symptoms of Pulmonary Tuberculosis

Respiratory symptoms	*Age groups*	*No. of patients*	*% of total*
No respiratory symptoms	Under 50	50	47·2
	Over 50	8	7·5
Cough	Under 50	56	52·8
	Over 50	98	92·5
Breathlessness	Under 50	13	12·3
	Over 50	33	31·1
Pain in chest	Under 50	15	14
	Over 50	23	21·7
Bloodstained sputum	Under 50	13	12·3
	Over 50	21	19·8
Frank hæmoptysis	Under 50	8	7·5
	Over 50	12	11·3
Hoarseness	Under 50	0	0
	Over 50	3	2·7
Non-respiratory symptoms			
No non-respiratory symptoms	Under 50	56	52·8
	Over 50	66	62·3
Weakness, lassitude	Under 50	30	28·3
	Over 50	55	51·8
Loss of weight	Under 50	37	34·9
	Over 50	53	50·0
Loss of appetite	Under 50	26	24·5
	Over 50	21	19·8
Ischio-rectal abscess	Under 50	0	0
	Over 50	2	1·9
Epigastric pain	Under 50	0	0
	Over 50	6	5·6
Symptom free: Mass X-ray, National Service and Contact X-ray, etc.	Under 50	33	31·1
	Over 50	8	7·5

Previous Illnesses and Associated Diseases

Patients over 50 could be expected to have a number of other illnesses besides pulmonary tuberculosis of which some might be chance associations.

Other Respiratory Disorders. Among 106 patients in this survey 1 had a neoplasm of the bronchus and another neoplasm of the larynx. Two patients had asthma all their lives and 2 had a pleural effusion 12 years ago and 20 years ago respectively. Only 1 patient had pneumoconiosis.

Mental Disease. Mild degrees of anxiety, irritability and depression are not infrequent symptoms of pulmonary tuberculosis, but 7 patients had received psychiatric treatment before the diagnosis of pulmonary tuberculosis.

Diabetes Mellitus. The incidence of diabetes mellitus requiring insulin was 5 (4·7 per cent.). This included 2 men and 3 women.

Liver Disease. Liver function tests (*i.e.*, estimation of thymol turbidity, serum bilirubin, serum proteins, urinary urobilinogen, serum electrophoresis) were performed on 22 patients. In 5 there was a combination of abnormally raised thymol turbidity and bilirubin values; 1 man had cirrhosis confirmed by liver biopsy and another had obstructive jaundice due to carcinoma of pancreas. In addition to these, 2 men had persistent abnormally raised urinary urobilinogen. Electrophoresis was performed on 4 patients in the acute stage of their disease and showed increased globulin and decreased albumen. It was performed on 16 patients at a later stage, during treatment, when 11 showed raised γ globulin.

Gastric Disease. The commonest association with the pulmonary tuberculosis in this series was peptic ulceration. Out of a total of 106 patients, 21 (19·8 per cent.) had a confirmed ulcer [6 (5·6 per cent.) gastric ulcer and 15 (14·1 per cent.) duodenal ulcer] before the diagnosis of active pulmonary tuberculosis. Two of these were females. Another 3 patients developed ulcers, 2 gastric and 1 duodenal, subsequent to the diagnosis. Thirteen had a partial gastrectomy at some time previous to the diagnosis (*vide* Table VI). Serial X-rays showed an acute exacerbation of previously inactive disease within 2 and 4 months after gastrectomy. One patient had an X-ray 3 years after gastrectomy, which was normal, but 7 years later showed gross tuberculous disease.

Although there were only 20 women 3 of these suffered from diabetes, 2 had a previous history of duodenal ulcer and 1 had abnormal liver function tests. Five other women were single and lived alone or in a hostel, 3 were recently widowed, lived alone and admitted seriously neglecting their meals, and 5 others were worried by recent illness or death of a near relative. Seven had a family history of pulmonary tuberculosis.

Previous X-rays

Fourteen patients (11 males and 3 females) had an apparently normal X-ray taken within 10 years of the diagnosis. A further 11 males had X-rays taken within 10 years of diagnosis which showed not more than a slight amount of inactive tuberculous disease at 1 or both apices.

TABLE VI.—GASTRIC DISEASE AND PULMONARY TUBERCULOSIS

		Condition before Ulcer			*Condition after Ulcer*			
No.	*Sex*	*Time of chest X-ray before ulcer*	*Zones affected*	*Ulcer*	*Opn. or med. trt. of ulcer*	*Time of chest X-ray after ulcer*	*Zones affected*	*Cav.*
1	M	Nil	—	G.U.	Gastrec'y	15 yrs.	2	+
2	,,	2 yrs.	1 (apex only)	,,	,,	1 yr.	5	—
3	,,	1 week	2 (both apices)	,,	,,	1 yr.	5	+
4	,,	Nil	—	,,	,,	(1) 3 yrs.	N.A.D.	—
						(2) 7 yrs.	4	+
5	,,	1 week	2 (LUZ. LMZ)	,,	,,	4 mths.	Inc. dis. LUZ. LMZ.	+
6	,,	Same time	N.A.D.	,,	Med. trt.	2 yrs.	3	+
7	,,	Nil	—	D.U.	Gastrec'y	13 yrs.	2	+
8	,,	Same time	2	,,	,,	2 mths.	3	—
9	,,	2 yrs.	1 (apex only)	,,	,,	1 yr.	2	—
10	,,	1 yr.	N.A.D.	,,	,,	7 yrs.	4	—
11	,,	Nil	—	,,	,,	10 yrs.	4	—
12	,,	,,	—	,,	,,	2 yrs.	4	+
13	,,	,,	—	,,	,,	9 mths.	2	—
14	F	,,	—	,,	,,	4 yrs.	3	+
15	M	,,	—	,,	Perf. repair	21 yrs.	4	—
16	,,	,,	—	,,	,,	3 yrs.	1	—
17	,,	,,	—	,,	,,	4 mths.	2	+
18	,,	,,	—	,,	Med. trt.	14 yrs.	2	—
19	,,	,,	—	,,	,,	6 mths.	3	—
20	,,	,,	—	,,	,,	4 yrs.	2	+
21	F	,,	—	,,	,,	8 yrs.	5	+

CONTACTS

Ninety-three patients (87·7 per cent.) had 1 or more adult home contacts which were radiographed. The total number of adult contacts examined was 210. These were mostly relatives living in close contact with the patient in the same house. Twenty-four adult contacts (11·4 per cent. of those examined), including 17 females and 7 males, were found to have active pulmonary tuberculosis requiring treatment. All except 3 females were close relatives. It was presumed that 4 of the elderly tuberculous patients had contracted the disease from other and younger members of the family (1 son, 1 daughter, 2 wives). The latter were discovered to have pulmonary tuberculosis, while the elderly patients were known to have had normal X-rays. Fifty-one child contacts under the age of 15 years were examined with X-rays and tuberculin tests. Twenty-six had negative tuberculin tests up to a strength of 1/100 tuberculin (100 T.U.) and received B.C.G. Twenty-five children had positive tuberculin tests and these included 1 with a pleural effusion and 2 with a primary tuberculous complex requiring treatment.

Family History

In the families of 23 patients (21·7 per cent.), including 16 male patients and 7 females, there were at least 1 or more persons known to have suffered from pulmonary tuberculosis, including the contacts previously mentioned. It is known that 6 parents, 5 siblings, 1 wife and 7 children had died from pulmonary tuberculosis.

Treatment

Chemotherapy

Eighty-seven patients in the present series were treated with chemotherapy only, 8 had surgical treatment and 11 had pneumoperitoneum. The earlier patients of this series received 1 G. Streptomycin sulphate daily and PAS 16-20 G. daily, and the Streptomycin was reduced to 1 G. three times weekly after the first three months. Later patients were usually given Streptomycin 1 G. intramuscularly daily, Isoniazid 200-300 mg. according to weight, daily, PAS 12-20 G. daily together, or two of these drugs were rotated in succession; after 3 months Isoniazid 200-300 mg. daily with PAS 12 G. daily was continued.

Patients Improved with Chemotherapy

Table VII summarises the radiological response of the disease, the rate of

Table VII.—Patients Improved with Chemotherapy
(67 *patients including* 25 *with cavities*)

	Total	*Months*											
		1-3	*4-6*	*7-9*	*10-12*	*13-15*	*16-18*	*19-21*	*22-24*	*25-27*	*28-30*	*31-36*	*Over 36*
Patients in whom drugs are continuing	39	0	12	7	8	3	2	2	2	1	1	1	
Patients in whom drugs have been stopped	28	0	3	4	6	5	5	2	2	1	0	0	
Patients followed up since stopping drugs	28	1	2	2	5	3	2	0	3	0	5	2	3 to 5 yrs.
Patients whose X-rays have ceased to show improvement	31	0	6	9	7	3	2	3	1				
Patients in whom sputum has converted	67	51	11	3	1					1			
Fate of cavities* 1-2·5 cm.	7		○○		● ●●	○		○					
2·6-4·0 cm.	16		●● ○○	●	●○ ○	●●	● ○	○	○●	○			
Over 4 cm.	2				○						●		

* Some of these patients have more than one cavity, in which case only the largest is considered here. All are confirmed by tomogram. The size refers to the greatest diameter.

○ = cavity still open. ● = cavity closed.

sputum conversion, and the fate of the cavities in the patients who have maintained improvement with continuous chemotherapy at the time of the survey. Sixty-seven patients are included in the table (59 males and 8 females) and 25 of these had cavities apparent in their X-rays and tomograms.

It will be noted that 39 are still continuing chemotherapy after varying periods of time. These include all those mentioned in this table who have cavities which remain patent and 6 of those patients with cavities which have closed. Twenty-eight have ceased chemotherapy and the length of their follow-up after cessation is stated. Among those who ceased chemotherapy are 6 patients with closed cavities. Their treatment stopped after periods of 10 to 12 months after cavity closure and they have been followed up for a further 6 months to 5 years.

None of the patients included in Table VII has relapsed. Of those in whom radiological stabilisation had occurred at the time of the survey, the maximal incidence was obtained between 7-9 months of treatment, but some improvement was still noted up to 24 months. The radiological extent of the disease of these patients was Class I, 12 patients; Class II, 33 patients; and Class III, 22 patients. So far, cavity closure has occurred up to 36 months and cavities which remains have all decreased in size. Sputum conversion occurred in all, including those with patent cavities.

TABLE VIII.—PATIENTS RELAPSED AFTER INITIAL IMPROVEMENT WITH CHEMOTHERAPY
(20 *patients including* 16 *with cavities*)

		Months								
	Total	*1-3*	*4-6*	*7-9*	*10-12*	*13-15*	*16-18*	*19-21*	*22-24*	
Patients having drugs prior to relapse	20	8	7	2	2				1	
Patients relapsed since end of drugs	20	2	0	2	5	2	2	1	5	(& 1=4 yrs.)
Patients whose X-rays ceased to show improvement	20	3	5	4	3					(5=ISQ)
Patients in whom sputum converted	20	7	3	2	1					7 persist positive
Fate of cavities 1-2·5 cm.	2	○	○							
2·6-4·0 cm.	10	○○ ○○	○ ○	○ ○	○ ○					
Over 4·0 cm.	4	○	○	○					○	

○=Cavity unclosed.

Fate of Patients who Relapsed after Chemotherapy

Table VIII shows that 20 patients (13 males and 7 females) relapsed. Most of these, who were treated in the earlier days of chemotherapy, had only short periods of chemotherapy, despite the fact that no cavities had closed and the sputum remained positive in some. Radiological improvement persisted for only a short time. The radiological extent of the disease was Class I, 2 patients; Class II, 10 patients; and Class II, 8 patients.

Ten improved clinically and radiologically with further chemotherapy. Two had drugs for periods of 1 year and 6 months, and 8 are still continuing chemotherapy after periods of 3 to 16 months. Eight of these patients have persistent cavities. The sputum remained negative in 5 patients, in 6 it reverted to positive on relapse but then became negative again, and in 3 it remained positive.

Three patients made a temporary improvement with further drugs after their relapse, but relapsed for a second time when these were stopped after periods of 3-12 months. Although the disease was checked by yet further drugs, which are being continued, a large extent of lung is now involved, and the sputum is persistently positive.

Seven patients became worse, 3 are very ill with very large cavities and 4 died.

Surgical Treatment

While on chemotherapy 8 patients with cavitated disease underwent surgical treatment with successful closure of the cavity and sputum conversion. Four men had a thoracoplasty, 1 man had a thoracoplasty with lobectomy and 2 women and 1 man had a lobectomy. Except for 1 man who had a hemiplegia and several relapses of the tuberculosis after lobectomy, and 1 man disabled by breathlessness, the operations were successful in controlling the disease.

Pneumoperitoneum. Eleven patients, 8 males and 3 females, had a pneumoperitoneum induced for cavitated disease and 7 of these had phrenic paralysis. Chemotherapy was continued for periods of 4 to 18 months. The pneumoperitoneum was abandoned after 2-4 years. All had cavities which were closed with this régime and the sputum became converted. Two patients with pneumoperitoneum who had chemotherapy for only 3 months relapsed but responded to further chemotherapy.

Complications of Treatment. Rash and fever considered to be due to streptomycin and P.A.S. occurred in 7 patients, 4 men and 3 women. These reactions appeared after intervals of 3 to 6 weeks from the beginning of the drugs. They ceased when both drugs were stopped in all except one man in whom a skin eruption persisted on the legs for 9 months. Two patients were desensitised and the drugs were then continued. Vertigo attributed to streptomycin occurred in 11 patients, 8 male and 3 female. Their ages ranged from 53 to 72 years. It was first noticed after 2 weeks of the drug (12 G.) in 3 patients, after 6 weeks (36 G.) in 3 patients and after periods varying from 7 to 12 months (90 G.—160 G.) in 3 patients. Awareness of the vertigo may have have been delayed until the patients started to walk about. It was mild and transient in 4 patients, moderate but persisting slightly after 2 years in 5, severe and persisting un-

changed for 1 year in 2 patients. Two patients became slightly deaf. In only 2 cases resistance to all 3 drugs was present among those in whom the sputum remained positive after 1 or more relapses of the disease.

Time in Hospital and Off Work

All the patients were admitted to hospital for investigation and initiation of treatment. Although the length of stay depended mainly on the severity of the disease, many patients were kept in hospital longer than necessary in view of inadequate home conditions. Some, despite extensive disease and cavitation, returned home after 3 months and successfully continued ambulant chemotherapy, but others stayed in hospital for as long as 12 months. Prolonged confinement to bed was avoided in view of their age, so that postural retention was limited. Those who eventually returned to work spent a further 4-12 months at home, though a few went to a convalescent institution, where they were able gradually to increase their activities indoors and outdoors and remain under supervision. Many patients could have resumed work earlier if suitable employment had been available.

Every case was known to the Health Visitors and Almoners who were able to offer advice and material assistance and supportive help, where the need for this was revealed, at all stages of treatment including rehabilitation. Diversional occupational therapy, also, was found to be beneficial and was made available in hospital and at home.

Table IX.—Re-employment

	Total ret. to work		*Former job*		*Former employees and lighter job*		*Different job*		*Still unfit*		*Retired*	*Died*
	S.	*N.S.*	*S.*	*N.S.*	*S.*	*N.S.*	*S.*	*N.S.*	*Due to P.T.*	*Due to other causes*		
Men	18	22	7	10	6	5	5	7	23	4	15	4
Women	1	0	1	0	0	0	0	0	9	0	10	0

S=Suitable. *N.S.*=Not suitable.

The above table summarises the extent to which these patients have taken up some form of employment by the time of the survey. A number have retired. In more than half of those who returned to work this was not considered suitable, because of health or income, but no adequate alternative could be found and some could not be re-employed.

Discussion

The present survey of 106 patients over the age of 50 with active pulmonary tuberculosis and positive sputum shows that the social classes 3, 4, and 5 yield the largest numbers, namely 19, 40 and 44 respectively. No obvious precipitating factor stood out to which the preponderance in these social classes might be attributable, but personal neglect, anxiety and delay in seeking medical advice

might have played a fundamental part. In addition, an understandable reluctance in considering the possibility of the diagnosis of pulmonary tuberculosis in these older patients who have a different pattern of symptomatology with the resultant lag in diagnosis is calculated to make the disease more prevalent in this group.

The symptomatology differs from those under 50 inasmuch as symptoms such as cough and breathlessness are more common in the older patients. Other common symptoms are chest pain, hæmoptysis, hoarseness and acute exacerbation of the chest symptoms, and while these might be compatible with less serious chest conditions the need for a careful assessment by a chest clinic arises if only to exclude bronchial neoplasm, quite apart from pulmonary tuberculosis. These symptoms which have been mentioned, however, are those of extensive disease, so that it is important to make the diagnosis at an earlier stage.

Owing to the dangers accruing to the normal population it becomes imperative to diagnose this group of patients at the inception of their symptoms. This is of especial importance in view of the possibility of spread of infection at work and elsewhere which is calculated to lead to an increase in primary infections, with their attendant morbidity, occurring in particular after school age. Only 7·5 per cent. of the cases of this series were symptom-free and were discovered by routine X-rays, compared with 31·1 per cent. of those under 50. Frequent mass radiography of persons of this group is clearly required.

Points of interest are the relative frequency of other diseases which may accompany and overshadow the respiratory tuberculosis in these patients. Seven had psychiatric treatment and 5 had been found to have diabetes mellitus before the tuberculosis was diagnosed. 19·8 per cent. had a peptic ulcer (5·6 per cent. gastric ulcer and 14 per cent. duodenal ulcer) and 13 of these cases had partial gastrectomy before diagnosis of the active tuberculosis, while in 2 with previously quiescent disease exacerbation occurred 2-4 months after the gastrectomy. The high incidence of liver disease in association with pulmonary tuberculosis described by Ban (1955) was not found in this series. Routine chest X-rays should be a standard practice in general hospitals investigating the aforementioned diseases in elderly patients. Electrophoresis findings were similar to those of Seibert and Nelson (1943).

Two hundred and ten adult home contacts were examined and among these 24 (11 per cent.) were found with active pulmonary tuberculosis. Twenty-six out of 51 children, many of them patients' grandchildren, were tuberculin negative. As evidence of the susceptibility of persons of this age group it is of interest that 4 patients appeared to have contracted their infection from others who were younger.

It is shown that improvement does occur with chemotherapy in spite of extensive and cavitated disease and the limited amount of bed rest considered advisable for patients of this age group. Maximal stabilisation of the X-ray appearances of infiltrative lesions is obtainable during the 7-9th month of chemotherapy and cavity closure is possible while sputum conversion is obtained usually by the end of 3 months of continuous treatment. Those in whom cavities remain patent do not usually relapse and their sputum remains negative as long as treatment continues. Bearing in mind the risks of

vertigo from streptomycin which may be very disabling in older persons, isoniazid and PAS seem to be the drug combination of choice for the continuation of treatment in ambulant patients, though careful supervision is required to ensure that both these drugs are being taken. Inactivity, mental or physical, is detrimental in old age. As soon as the sputum has converted and the general health permits it would appear that some form of gainful employment may be resumed by those who are not retired. Time in hospital should be as short as possible provided that home conditions are satisfactory.

While these patients may not be always able to continue with their previous employment, many may still undertake productive work in a less active capacity or under sheltered conditions. Sheltered workshops embodying these features are obviously necessary, but unfortunately there are as yet only too few suitable examples.

The incidence of pulmonary tuberculosis among older persons has been discussed by Stocks (1949), Springett (1952), Benjamin (1953), McDonald and Springett (1954), Joint Tuberculosis Council (1955) and the clinical features by Hebbert (1948) and Wilkins (1956). The observations concerning the association of pulmonary tuberculosis with peptic ulcer and partial gastrectomy concur with those of Pulvertaft (1952), Anderson, Gunn and Watt (1955), Thorn, Brookes and Waterhouse (1956). The results of prolonged chemotherapy of the patients in this series are in agreement with those described by Clarke (1952), Doonief and Hite (1954), Steiniger and Howard (1955), Hoyle, Nicholson and Dawson (1955), Ross and Kay (1956) and Douglas and Horne (1956).

The problems of re-employment of these older tuberculous persons have been discussed by Mathers (1954), Marsh (1955), and *Lancet* (1955) and these views are consistent with similar experiences among patients in the present series.

Summary

One hundred and six patients over the age of 50 with pulmonary tuberculosis have been studied. The social factors, clinical pattern and associated conditions have been discussed.

Continuous chemotherapy over indefinite periods was found to control the disease and permitted a number to return to work.

The need for improved case finding, including mass X-rays and the increasing importance of facilities for suitable re-employment have been emphasised.

We wish to thank Dr. H. J. Anderson and Dr. D. S. Cadman for permission to study their cases and for their valuable criticism, and Dr. W. J. Griffiths and his staff for carrying out liver function tests. We are greatly indebted to the Almoners, Health Visitors and Occupational Therapists for furnishing valuable social information and suggestions.

REFERENCES

Anderson, C. D., Gunn, R. T. S., and Watt, J. K. (1955): *Brit. med. J.*, **1**, 508.
Ban, B. (1955): *Amer. Rev. Tuberc.*, **72**, 71.
Benjamin, B. (1953): *Brit. J. Tuberc.*, **47**, 4.
Clarke, O. (1952): *Brit. med. J.*, **2**, 644.
Doonief, A. S., and Hite, K. E. (1954): *Amer. Rev. Tuberc.*, **70**, 219.
Douglas, A. C., and Horne, N. W. (1956): *Brit. med. J.*, **1**, 375.

FOSTER-CARTER, A. F., MYERS, M., GODDARD, D. L. H., YOUNG, F. H., and BENJAMIN, B. (1952): *Brompton Hosp. Rep.*, **21**, 1.
HEAF, F. R. G. (1955): *J. Roy. Inst. Publ. Hlth.*, **18**, 324.
HEBBERT, F. J. (1948): *Lancet*, **2**, 247.
HOYLE, C., NICHOLSON, H., and DAWSON, J. (1955): *Lancet*, **2**, 1310.
JOINT TUBERCULOSIS COUNCIL (1955): "The Changing Character of Tuberculosis." Pub. by the Joint Tuberculosis Council.
Lancet (1955), **2**, 546.
MCDONALD, J. C., and SPRINGETT (1954): *Brit. med. Bull.*, **10**, 77.
MARSH, K. (1955): *Med. Offic.*, **94**, 31.
MATHERS, R. GRENVILLE (1954): *Brit. med. Bull.*, **10**, 87.
MINISTRY OF HEALTH REPORT (1955): Pt. II, H.M.S.O., London, p. 232.
PULVERTAFT, C. N. (1952): *Lancet*, **1**, 225.
ROSS, J. D., and KAY, D. T. (1956): *Thorax*, **11**, 1.
SEIBERT, F. B., and NELSON, J. W. (1943): *Amer. Rev. Tuberc.*, **47**, 66.
SPRINGETT, V. H. (1952): *Lancet*, **1**, 521.
STEINIGER, W. J., and HOWARD, W. L. (1955): *Dis. Chest*, **28**, 177.
STOCKS, P. (1949): *Tubercle (Lond.)*, **30**, 50.
THORN, P. A., BROOKES, V. S., and WATERHOUSE, J. A. H. (1956): *Brit. med. J.*, **1**, 603.
WILKINS, E. G. (1956): *Brit. med. J.*, **1**, 883.

THE LONG-TERM RESULTS OF THE TREATMENT OF PULMONARY TUBERCULOSIS BY PNEUMOPERITONEUM

By Arnold Pines

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"Despite the size of the bibliography, there is all too little concrete evidence on which to weigh the effectiveness of pneumoperitoneum. The existing literature is lacking in detailed reports of this treatment followed over long periods" (Mitchell *et al.*, 1947).

The follow-up for short periods only of methods of treatment in pulmonary tuberculosis may give fallacious results, while observation for longer periods

Author	*Number*	*Extent of disease in majority*	*Maximum observation period*	*Proportion so observed*	*Final evaluation of P.P.*
1938					
Bennett	200	Far advanced	2 years	Most	Poor
Stokes	41	Far advanced	2 years	Some	Poor
1939					
Centoscudi *et al.* ..	30	?	4 years	Most	Fair
Mellies	93	Far advanced	3½ years	Some	Good
1940					
Boislinière	50	Far advanced	1½ years	Some	Moderate
1941					
Dongrey	38	Far advanced	2 years	Some	Fair
Fowler	56	Mixed	3 years	Some	Fair
Sanchez Acosta *et al.* ..	50	Mixed	?	—	Fair
1943					
Clifford Jones *et al.* ..	60	Far advanced	2 years	Some	Fair
Mallick *et al.*	156	Far advanced	2 years	Few	Fair
1944					
Rilance *et al.*	101	Mixed	3-5 years	One third	Fair
1945					
Browne *et al.*	45	Mixed	?	—	Moderate
Edwards *et al.*	50	Far advanced	1¼ years	Few	Moderate
Crow *et al.*	546	Mixed	5 years	Few	Fair
Anderson *et al.*	110	Mixed	4 years	Few	Good
1947					
Mitchell *et al.*	474	Far advanced	5 years	Few	Fair
Hurst *et al.*	75	Mixed	Short	—	Fair

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may show that such methods prolong life little more than bed rest alone (Cold, 1937; Thompson, 1942; Mann, 1948).

The poverty of the literature on pneumoperitoneum in this respect is conveniently shown in tabular form below. In this table, the relevant features of the larger and more important published series have been broadly outlined: these papers and many others on pneumoperitoneum therapy have been criticised in detail elsewhere (Pines, 1956 (a)). It was in consequence of this lack of long-term assessment that the present work was undertaken.

Author	*Number*	*Extent of disease in majority*	*Maximum observation period*	*Proportion so observed*	*Final evaluation of P.P.*
1948					
Keers	74	Mixed	?	—	Fair
Trimble *et al.**					
1949					
Hanrahan	57	Mixed	Short	—	Good
1950					
Habeeb *et al.*	100	Mixed	2 years	Most	Good
Matas *et al.*	100	Mixed	?	?	Good
Figueiredo *et al.* ..	122	Far advanced	Short	—	Fair
Sita Lumsden	125	Mixed	2 years	Most	Good
1951					
Williams	226	?	2-7 years	All	Good
Netzer	246	Far advanced	Short	—	Poor
Bernard *et al.*	70	Mixed	Short	—	Fair
Bariety	75	Mixed	Short	—	Fair
Kourilsky *et al.*	90	Mixed	Short	—	Fair
1952					
Bornstein *et al.*	106	Far advanced	Short	—	Fair
Yek	190	Mixed	2-10 years	All	Good
Cervia	116	Mixed	?	—	Good
Crenshaw *et al.**					
1953					
Edge*					
Rebora	222	Mixed	?	—	Fair
1954					
David	178	?	3-4 years	Some	Good
Brinkman *et al.*	21	Mixed	Short	—	Useful
1955					
Livingstone*					

**Vide infra.*

The Investigation

Method. The scope of this study demanded a follow-up of at least six and a half years. The years chosen for analysis, therefore, were 1945 to 1947, when P.P. was in maximal use at Harefield Hospital, where all these patients had been treated. Consequently, streptomycin was not used initially in any of these patients and in comparatively few during after-years.

All cases of primary pneumoperitoneum were included and also those where a pneumothorax had been tried, but had failed and had been promptly abandoned. In all, the P.P. had been maintained for at least three months. Three-hundred and thirty-four cases of P.P. were recorded, 287 were fully traced and 225 confirmed to the preceding criteria. In nearly half a phrenic crush had been performed. Follow-up was by personal interview in almost half and in the remainder by a questionnaire, which was completed by the appropriate chest physician. All relevant X-rays were examined.

Results

The survivors of the whole series were observed for a period varying from six and a half to nine and a half years without exception. By the beginning of 1945 one-quarter had died (26 per cent.).

Prognosis in pulmonary tuberculosis is very closely related to the extent of disease at the time when treatment is begun (Foster-Carter *et al.*, 1952; Mitchell, 1955). Moreover, "the one real ponderable in pulmonary tuberculosis is mortality" (Shaw, 1933). Mortality in the present series corresponded to the extent of disease immediately before the induction of the P.P., as is shown in the following table:

*Extent of disease**	*Number*	*Alive*		*Dead*	
		No.	%	*No.*	%
Minimal	12	12	100	0	0
Moderately advanced	157	130	83	27	17
Far advanced	56	24	43	32	57

* The classification used has been that of the National Tuberculosis Association of America.

The necessity of observing these patients for at least three and preferably at least five years is clear:

	Time of Death *Years after induction of P.P.*								
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
No.	28	15	18	3	3	0	0	2	0

Comparison with results of other authors is difficult. As has been previously shown, there are few analyses available of patients treated with pneumoperitoneum who were consistently observed for several years or more, and certainly

none where this period was a minimum of six and a half years, as in the present series. The findings of those who have analysed the ultimate fate of their cases may be conveniently presented in the following table:

Author	*Observation period*	*Extent of disease*	*Total*	*Alive*		*Dead*	
				No.	%	*No.*	%
Trimble *et al.* (1948)	4 years+	Combined	382	309	71	73	19
Crenshaw and Gross (1952)	Many for 4 years	Combined	579				
		Mod. advanced	210	198	94	12	6
		Far advanced	337	245	70	92	30
Edge (1953)	4-9 years	Combined	101	76	75	25	25
Livingstone (1955)	3-11 years	Combined	68	56	82	12	18
		Mod. advanced	24	20	84	4	16
		Far advanced	26	19	73	7	27

The prognoses of the patients treated by Trimble *et al.* and by Edge have, unfortunately, not been analysed in relation to extent of disease. They cannot adequately, therefore, be compared to the present series.

A large proportion of Grenshaw and Gross's patients had been observed for one or two years only, and consequently their low mortality is fallacious.

Livingstone's personal series was small and selection may have played a part in his good results. It is most probable, nevertheless, that the primary factor was his personal supervision of all these patients, from diagnosis throughout the whole course of their treatment and of their disease.

The prognosis appears to have been definitely worse in the patients treated at Harefield Hospital, even when those with similar extents of disease are compared. It is possible that the Harefield cases were a less selected group and had more acute and toxic disease when admitted. These factors may have had a corresponding effect on mortality.

Prognosis in Relation to Relatively Untreated Pulmonary Tuberculosis

To establish any value of pneumoperitoneum treatment as used in the cases which have been studied, comparison must be made with what has been called the "natural" prognosis of pulmonary tuberculosis—*i.e.*, those in whom collapse therapy had not been attempted. Ideally, such cases should have been found at Harefield Hospital in the years studied, but it soon became clear that only a few patients fell into this category. In despite, therefore, comparison must be made with the published prognosis of untreated pulmonary tuberculosis.

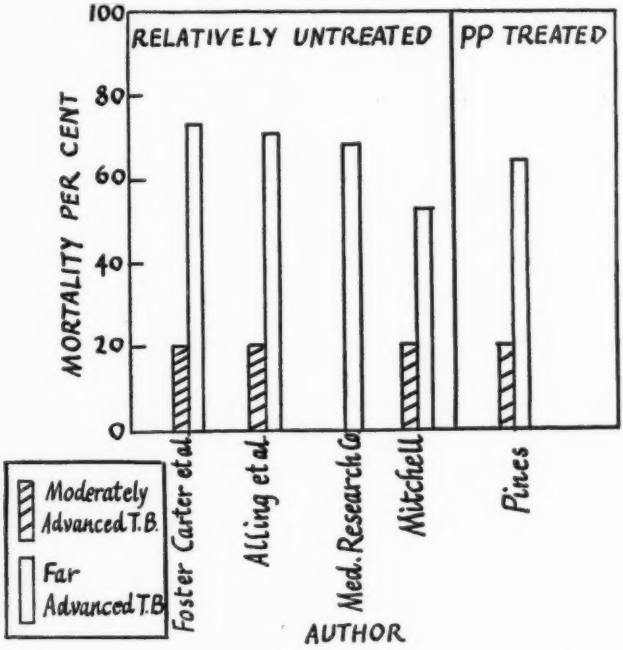
The appalling ultimate fate of their patients described by Thompson (1942) and Tattershall (1947) was exceptional and probably influenced by various local factors. Recent publications on long-term prognosis have shown a remarkable concordance in their results.

From the concordance of these results, it may be deduced that, in Great Britain and the United States, with moderately advanced disease the ultimate mortality may be expected to be roughly 20 per cent. With far advanced disease, mortality will be roughly 70 per cent. (Mitchell's cases were "relatively

Author	*Observation period*	*Mortality*	
		*moderately adv.**	*Far advanced**
Foster-Carter *et al.* (1952) (controls)	8 years	19%	75%
Alling *et al.* (1954 and 1955) ..	10 years	20%	70%
Medical Research Council (controls) (1955)	5 years	—	68%
Mitchell (1955)	15-25 years	20%	50%

* Definitions of disease have been standardized.

selected"). These mean results for largely untreated pulmonary tuberculosis may therefore be compared to the results of pneumoperitoneum in the present investigation in relation to comparable extents of disease. With moderately advanced disease, no significant difference emerges, while with far advanced diseases there may have been some slight benefit from treatment.



It may be objected that the patients treated at Harefield Hospital constituted an unusually selected group. From personal knowledge of local conditions this seems unlikely. In any case, all the series referred to immediately above were of groups of patients selected in various ways. Nevertheless, time and number largely erased all such differences, as has been shown.

Again, some of the "milder" admissions may have been treated successfully by primary pneumothorax, so that the cases treated by pneumoperitoneum

constituted a more severely affected group. If pneumoperitoneum had been used more indiscriminately to include these " milder " lesions, overall results might possibly have been better than in the present series. But it is still very unlikely that they would have been much improved.

Clinically, there were undoubtedly many patients where P.P. had given some benefit. Unfortunately there were also many where disease had undoubtedly deteriorated only after the commencement of pneumoperitoneum therapy. This was particularly clear where lobar collapse and bronchogenic spread occurred as complications. As is obvious from the table showing the time of death, the use of pneumoperitoneum did not even prolong life in the vast majority of those patients who died. These aspects have been analysed in detail elsewhere (Pines, 1956 (b)).

Pneumoperitoneum treatment, therefore, had little demonstrable effect upon survival in this series of patients. It is not, consequently, a primary treatment of value in pulmonary tuberculosis.

Indications and Contra-Indications

In certain types of disease, improvement or conversely deterioration were particularly marked, so that relative indications and contra-indications may be formulated.

Indications

Isolated cavitation or limited infiltration, particularly in the lower lobes.
Limited value. Predominantly fibrotic disease.
No value. Solid lesion.

Contra-indications

The following conditions have been shown to lead to lobar collapse and to a very high incidence of spread (Pines, 1956 (b)):

(*a*) Extensive disease with a predominantly exudative element.
(*b*) Cavitation with surrounding consolidation or infiltration of lobar extent.
(*c*) Where lobar collapse has already taken place and endobronchial disease is still active.

Often in such disease, peripheral lesions may regress with the use of pneumoperitoneum, so that surgery to the original lesion becomes possible. But the risk of aggravation of such disease by the use of pneumoperitoneum is also high (Pines, 1956 (b)). (In contemporary treatment, the preliminary use of two or three months of chemotherapy will usually, but not invariably, avoid these dangers.)

Where the use of pneumoperitoneum appears to control the lesions satisfactorily, it is essential to maintain the pneumoperitoneum for at least four years, to ensure arrest. Premature abandonment, in this series, caused relapse in a high proportion of cases.

Summary

The literature on pneumoperitoneum is largely lacking in reports of long-term results.

Two hundred and twenty-five patients treated by primary pneumoperitoneum have been followed for six and a half to nine and a half years. Apart from the choice of therapy, they were unselected. Twenty-six per cent. died by the end of the observation period.

In relation to extent of disease, 17 per cent. of those who had moderately advanced disease died, as did 57 per cent. of those who had far advanced lesions. These results have been compared with the published results of series treated largely by bed rest alone in relation to comparable extents of disease. There is little or no significant difference in their ultimate fate.

Pneumoperitoneum treatment, therefore, had little demonstrable effect upon survival in this series of patients. It is not, consequently, a primary treatment of value in pulmonary tuberculosis.

(1) This paper summarises part of a thesis accepted for the degree of M.D., University of Cambridge.

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(3) I am particularly indebted to Dr. B. Benjamin for his statistical advice and approval of results.

REFERENCES

Alling, D. W., Lincoln, N. S., and Bosworth, E. B. (1954): *Amer. Rev. Tuberc.*, **70,** 995.
Alling, D. W., Lincoln, N. S., and Bosworth, E. B. (1955): *Amer. Rev. Tuberc.*, **71,** 519.
Anderson, N. W., and Winn, W. D. (1945): *Amer. Rev. Tuberc.*, **5,** 380.
Bariety, M. *et al.* (1951): *Rev. Tuberc. (Paris)*, **15,** 113.
Bennett, E. S. (1938): *Lancet*, **58,** 157.
Bernard, E. *et al.* (1951): *Rev. Tuberc. (Paris)*, **15,** 7.
Boislinière, L. C., Boucek, J. J., Gerson, C. E., and Henske, A. C. (1940): *J. Miss. med. Ass.*, **37,** 337.
Bornstein, P. K., and Graber, I. (1952): *Quart. Bull Sea View Hosp.*, **13,** 149.
Brinkman, G. L., Raleigh, J., and Mitchell, R. S. (1954): *Amer. Rev. Tuberc.*, **69,** 693.
Browne, N. C., and Corrigan, F. L. (1945): *Irish J. Med. Sci.*, **6,** 697.
Centoscudi, C., and Agostino, A. (1939): *Riv. Patol. Clin. Tuberc.*, **13,** 347.
Cervia, T., Dominquez, J., and Delgado, J. R. (1952): *Rev. clin. esp.*, **47,** 28.
Clifford-Jones, F., and MacDonald, N. (1943): *Tubercle (Lond.)*, **24,** 97.
Cold, S. (1937): *Acta Tuberc. Scand.*, **11,** 63.
Crenshaw, F., and Gross, J. H. (1952): *Dis. Chest*, **22,** 91.
Crow, H. E., and Whelchel, F. L. (1945): *Amer. Rev. Tuberc.*, **5,** 367.
David, J. D. P. (1954): *Tubercle (Lond.)*, **35,** 90.
Dongrey, L. R. (1941): *Indian med. Gaz.*, **76,** 587.
Edge, J. R. (1953): *Brit. J. Tuberc. Dis. Chest.* **97,** 202.
Edwardes, P. W., and Logan, J. (1945): *Tubercle (Lond.)*, **26,** 11.
Figueiredo, F. P. de, *et al.* (1950): *Rev. Bras. Tuberc.*, **18,** 513.
Foster-Carter, A. F., Myers, M., Goddard, D. C. H., Young, F. H., and Benjamin, B. (1952): *Brompton Hosp. Rep.*, **21,** 3.
Fowler, W. O. (1941): *Amer. Rev. Tuberc.*, **44,** 474.
Habeeb, W. J., and Reisner, H. G. (1950): *Amer. Rev. Tuberc.*, **61,** 323.
Hanrahan, M. (1949): *Irish J. Med. Sci.*, **6,** 112.
Hurst, A., Maier, H. M., and Dwork, W. (1947): *Dis. Chest*, **13,** 345.
Keers, R. W. (1948): *Brit. J. Tuberc. and Dis. Chest*, **92, 58.**
Kourilsky, R., Lemanissier, A. F., Vicaire, J., and Fuchon, P. (1951): *Sem. Méd. (Paris)*, **27,** 799.
Livingstone, J. L. (1955): *Brit. Med. J.*, **1,** 243.
Mallick, S. M. K., Malkotra, C. L., and Mohammad, N. (1943): *Tubercle (Lond.)*, **24,** 165.
Mann, B. (1948): *Tubercle (Lond.)*, **29,** 131.

MATAS, M., and BARCLAY, W. R. (1950): Med. papers, 50th Ann. Meeting, Canad. Tuberc. Ass., 70.
MELLIES, C. J. (1939): *J. Miss. med. Ass.*, **36,** 430.
Medical Research Council (1955) quoted by Livingstone, *op. cit.*
MITCHELL, R. S., HIATH, J. S., MCCAIN, P. P., EASOM, H. F., and THOMAS, C. D., (1947): *Amer. Rev. Tuberc.*, **4,** 301.
MITCHELL, R. S. (1955): *Amer. Rev. Tuberc.*, **74,** 487.
Nat. Tuberc. Ass. of America, " Diagnostic Standards," N. York, 1950.
NETZER, S. (1951): *Amer. Rev. Tuberc.*, **63,** 62.
PINES, A. (1956 a): M.D. Thesis, Cambridge University Library.
PINES, A. (1956 b): *Brit. J. Tuberc. Dis. Chest*, **50,** 346.
REBORA, F. (1953): *Rev. Mex. Tuberc.*, **14,** 487.
RILANCE, A. B., and WARRING, F. H. (1944): *Amer. Rev. Tuberc.*, **49,** 353.
SANCHEZ ACOSTA, R., ARANDA GOMEZ, I., and DIAZ, J. P. (1941): *Rev. Tuberc. (Habana)*, **5,** 85.
SHAW, C. (1933): *Brompton Hosp. Rep.*, **2,** 48.
SITA LUMSDEN, E. G. (1950): M.D. Thesis, Cambridge University Library.
STOKES, J. B. (1938): *Illinois med. J.*, **73,** 137.
TATTERSALL, W. H. (1947): *Tubercle (Lond.)*, **28,** 107.
THOMPSON, B. C. (1942): *Tubercle (Lond.)*, **23,** 139.
TRIMBLE, H. G., EATON, J. L., CRENSHAW, G. L., and GORLEY, E. (1948): *Amer. Rev. Tuberc.*, **5,** 433.
WILLIAMS, E. (1951): *Tubercle (Lond.)*, **32,** 26.
YEK, J. (1952): *Canad. med. Ass. J.*, **66,** 553.

LOBAR COLLAPSE FOLLOWING PNEUMOPERITONEUM IN PULMONARY TUBERCULOSIS

ITS INCIDENCE AND SIGNIFICANCE

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The significance of atelectasis* in pulmonary tuberculosis has remained disputed since its first recognition (Packard, 1928; Habliston, 1928). Some have considered that it was a benign phenomenon and that it contributed to cavity closure (Hennell, 1931; Glenn, 1931; Coryllos, 1933, 1936; Eloesser, 1937; Pagel and Simmonds, 1939, 1942). Others have regarded it as marking deterioration, contributing to the persistence of cavities and to bronchogenic spread (Rafferty, 1943; Cuthbert and Nagley, 1948; Coello and Nagley, 1948; Houghton, 1950). Yet others have held that it was the persistence of cavities rather than atelectasis in itself which was deleterious (Farquharson, 1951; Foster-Carter and others, 1952; Sadler, 1954). Benign and malignant forms of atelectasis have also been distinguished (Coello, 1951; Temple, 1955).

In artificial pneumothorax treatment, the phenomenon has been frequently described. Again, it has been regarded as beneficial (Brooks, 1938; Erwin, 1939), or as of no importance (Foster-Carter and others, 1952; Scadding and others, 1952; Sadler, 1954). Many, however, have associated its onset with relapse and with empyema (Rafferty, 1943; Houghton, 1950; Maher-Loughnan, 1950; Mitchell, 1951).

With pneumoperitoneum, in contrast, atelectasis has been noted only occasionally and has usually been considered as unimportant (Stokes, 1938; Mellies, 1939; Itturriaga, 1942; Crow and Whelchel, 1945; Banyai, 1946; Fegiz, 1946; Houghton, 1950; Williams, 1951; Lachance, 1952; MacDonald, 1952; Bobrowitz, 1953; David, 1954). The largest series consists of twenty cases (Farquharson, 1950). That in reality lobar collapse is frequent and that it may be of the gravest import will be shown in the following investigation.

The Investigation

I first noticed the frequency of the phenomenon in pneumoperitoneum while examining a number of serial X-rays for another study (Pines, 1954). This frequency seemed contrary to the scanty published references, and the subject therefore seemed worthy of study. Further, it became obvious that lobar collapse was, in some of these cases, associated with rapid and unexpected deterioration.

* Atelectasis and absorption collapse have been regarded as synonymous throughout.

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Method

All cases of primary pneumoperitoneum were studied who had been treated at Harefield Hospital during the years 1944 to 1947, when pneumoperitoneum was most widely used in this hospital. The very few patients who had received streptomycin in 1947 were excluded; similarly, a survey of such patients from 1948 and onwards was abandoned because of obvious statistical difficulties (*vide infra*). Follow-up was by personal interview or by questionnaire completed by the appropriate Clinic Chest Physician: survivors were followed for from six and a half to ten years (to the beginning of 1954). No case was included who had had less than three months' pneumoperitoneum treatment or who had received previous pneumothorax therapy of any duration.

There were 431 cases recorded where pneumoperitoneum had been used during 1944-47; 370 were traced and of these 298 fulfilled the above criteria and were studied.

X-ray Diagnosis of Lobar Collapse

When collapse of an upper lobe was diagnosed, the classical criteria (Coope, 1948) including tracheal shift were observed in five-sixths of these cases. In the remaining one-sixth there was, as with the others, contraction of the affected lobe to two-thirds or less, with corresponding displacement of septa, of the hilum and of vascular markings. Though there was no tracheal displacement in these latter, the diagnosis of lobar collapse is consistent with the definition of many modern authorities (Golden, 1941; Rafferty, 1943; Bishop, 1946; Kerley and Twining, 1951).

When lower lobe collapse was diagnosed, there were similar changes. In some there was shift of the heart to the affected side. In others, there was no such displacement because the raised paralysed hemi-diaphragm took up most of the area of the hemi-thorax vacated by the collapsed lobe.

It has been clearly shown that pneumoperitoneum and paralysis of one hemi-diaphragm cause a definite shift of the mediastium towards the opposite side (Fox, 1950). That the reverse has taken place in the above cases conclusively confirms the diagnosis of lobar collapse in them.

In none was there much re-expansion of the collapsed lobe even when the P.P. had been abandoned, indicating that simple lung compression was not responsible for the above changes.

(1) General Features

(a) Incidence

In the whole group of 298 suitable cases of pneumoperitoneum, lobar collapse took place in over a third, in 104. In 94 the phrenic nerve was crushed on one side. There are no comparable series which attempt to assess the frequency of lobar collapse following pneumoperitoneum, but this incidence corresponds with that found in several series of pneumothoraces (MacDonald, 1952; Scadding and others, 1952; Brinkman, 1953), the common factor being almost certainly tuberculous endobronchitis (*vide infra*).

(b) Lobar Distribution

Among these 104 cases, there were 93 with upper lobe and 17 with lower lobe collapse. In 6, two lobes were affected. There was no definite case where the middle lobe collapsed. The distributions of the involved lobes correspond closely to those found by Farquharson (1950):

Author	*R.U.L.*	*L.U.L.*	*R.L.L.*	*L.L.L.*
Farquharson	70	38	14	7
Pines	60	33	7	10

There is no convincing explanation for this incidence, which does not correspond to the usual frequency of disease in each lung or lobe (Dunham, 1917; Sweany and others, 1931), nor to those recorded by other writers (Salkin, 1936; Himalstein, 1951) who considered that collapse of the lower lobes was commonest.

There was no difference in the ultimate prognosis of lesions in the left as compared to the right lung (*cf.* Mitchell, 1955).

(c) State of the Affected Lobes

In most, exudative disease was predominant before the induction of pneumoperitoneum. This appeared in the X-ray as a dense opaque area, or as cavitation with extensive surrounding infiltration in which aerating portions of lung tissue intermingled, both occupying most or all of a lobe or lobes. These appearances represent tuberculous consolidation, with mixed caseation and exudation (Pinner, 1937; Cuthbert and Nagley, 1948; Coello and Nagley, 1948), which has been held by many writers to be the type of disease which responds best to P.P.

In the 104 cases, the state of the affected lobes was as follows:

Type of disease	*No.*
Exudative	86
Previous collapse increased	11
Isolated cavitation	7

Again, if in the sample year 1946 lobar collapse is related to the broad types of disease met in all cases treated by P.P. during that year, then once more exudative disease appears as the outstanding forerunner of collapse:

Type of disease	*Total*	*Complicated by lobar collapse*
Exudation	26	23
Previously collapsed	6	4 (increased collapse)
Isolated cavitation	22	2
Infiltration without cavitation or consolidation ..	19	0

Definite evidence of tracheo-bronchial tuberculosis was found in 22 patients by laryngoscopy (in 9) or bronchoscopy (in 13). In the remainder, broncho-

scopy had not been performed and might well have revealed further cases. In many, however, endo-bronchitis probably involved predominantly the smaller bronchi (Pinner, 1937; Loeschcke, 1938; Cuthbert and Nagley, 1948; Jones and Alley, 1951) and could not have been seen.

(d) Time of Collapse

Disease was present for a mean ten months before the induction of the pneumoperitoneum (time as estimated from the diagnostic X-ray), while collapse of the lobe occurred at a mean two months after induction (varying from one to sixteen weeks). Since collapse had not taken place during this long period before pneumoperitoneum induction but only within a short time afterwards, the close relationship of this collapse to the commencement of the pneumoperitoneum becomes obvious.

2. Prognosis according to Certain Features before Induction of P.P.

(a) Sex and Age

Mortality was highest in women aged 15 to 30 years. This merely corresponds to the general mortality for tuberculosis in England and Wales during 1944-47 (Registrar-General, 1944-47).

(b) Cavitation

Where cavitation was present, mortality was far higher:

Disease state	*No.*	*Alive*		*Dead*	
		No.	%	*No.*	%
Cavitation present	87	49	56	38	44
Cavitation absent	17	14	82	3	18

(c) Contra-lateral Disease

Where disease was present in the lung opposite to that where the major lesion lay, the mortality was high, particularly when cavitation was present.

Disease state	*No.*	*Alive*		*Dead*	
		No.	%	*No.*	%
Contra-lateral infiltration only ..	53	27	51	26	49
Contra-lateral cavitation	10	2	20	8	80
No contra-lateral disease present ..	41	34	83	7	17

(d) Relationship of Preliminary Bed Rest to Prognosis

The mean period of bed rest before the induction of the pneumoperitoneum was five months. To assess the significance of bed rest, the mean prognosis of those treated with less than this five months' rest was compared with that of those who had remained in bed for a longer period:

Period of bed rest	*No.*	*Alive*		*Dead*	
		No.	%	*No.*	%
Less than five months	59	41	69	18	31
More than five months	45	22	49	23	51

Prolonged bed rest, therefore, may have had no effect on prognosis. The possible errors of this conclusion have been discussed elsewhere (Pines, 1956).

3. Prognosis according to Certain Features after the Induction of P.P.

(*a*) *The Prognosis of those with Lobar Collapse compared to those without Lobar Collapse, in Relation to Extent of Disease*

It is generally agreed that the prognosis of an individual patient with pulmonary tuberculosis may be closely related to the total volume of lung which is diseased, varying directly with the extent of involvement (Foster-Carter and others, 1952; Mitchell, 1955). The classification used here has been that of the National Tuberculosis Association of America (1950), which is perhaps the most convenient and the most widely used.

The prognosis of the collapsed group of 104 patients may thus be fairly compared to that found in the control group of 144 patients where no lobar collapse had occurred (these latter comprised all such patients from the years 1945-47) in relation to comparable extents of disease. Their respective fates six and a half to ten years after induction of pneumoperitoneum were as follows:

Group	*No.*	*Alive*		*Dead*	
		No.	%	*No.*	%
Collapsed					
Moderately advanced	69	49	71	20	29
Far advanced	35	14	40	21	60
Not collapsed					
Moderately advanced	106	92	87	14	13
Far advanced	26	12	46	14	54

From these results there would appear to be little difference in the fate of the far advanced cases in both groups. But in the moderately advanced cases the mortality in the collapsed group is more than twice that found in the control cases, although they had comparable volumes of diseased lung. *It is valid to conclude that with disease of this extent collapse of a lobe was a markedly adverse factor.*

The importance of following these patients for at least three and preferably five years is shown in the following table:

Series	Time of death (both groups) — Years after P.P. inductions								
	1	2	3	4	5	6	7	8	9
Collapsed cases	18	7	10	3	1	0	0	2	0
Non-collapsed (control) cases	10	8	8	0	2	0	0	0	0

(b) The Clinical Results of Treatment

Four broad clinical divisions became obvious when the collapsed lobe series was analysed. In the first, the disease appeared to be fully and permanently controlled by the P.P. In the second, P.P. at no time exerted much control over the lesion and other measures had to be adopted. In the third, bronchogenic spread into the same or opposite lung followed precipitously the onset of atelectasis. In the fourth, control seemed to have been established, but relapsed quickly followed the premature abandonment of the pneumoperitoneum.

The following table gives their essential prognosis (in four cases, results were such that they fell into two categories):

PROGNOSIS IN RELATION TO THE RESULTS OF TREATMENT

Group	No.	Well and working		Invalid		Dead	
		No.	%	No.	%	No.	%
Controlled by P.P.	23	22	96	1	4	0	0
Not controlled by P.P.	39	28	72	6	15	5	13
Spread after P.P.	36	5	14	1	3	30	83
Relapse after P.P.	10	1	10	3	30	6	60

The very widely differing fate of each group substantiates their clinical distinctness.

There was little difference among the groups in relation to mean duration of disease, of bed rest and of the time elapsing between pneumoperitoneum induction and atelectasis:

Group	Mean duration of disease* before P.P.	Mean bed rest before P.P.	Mean period before collapse
	Months	Months	Months
Controlled by P.P. ..	10	5·5	2·2
Not controlled by P.P. ..	11	4·3	2·2
Spread after P.P.	11·4	5·4	2·1
Relapse after P.P. ..	7	4·6	2·5

* Duration of disease estimated from the date of the diagnostic X-ray.

There were no obvious differences in the initial type of disease met among the groups.

(i) *Disease controlled by P.P.* In 23 cases, cavitation and consolidation cleared permanently, usually within six months but in a few after fourteen to eighteen months. The collapsed lobe in no case re-expanded and its X-ray signs remained permanent. In none was there bronchogenic spread.

All these patients were alive and well in 1954. The mean period of maintenance of the pneumoperitoneum was 4·2 years (in only four patients was it three years) and it is clear that this long maintenance period was a principal factor in the survival of these patients: this becomes particularly obvious when this group is compared to the relapsed group (iv), where the short maintenance period (mean 1·9 years) was chiefly responsible for such relapse.

A much larger proportion of lower lobe (more than half) than of upper lobe cases (roughly 1/10) did well with pneumoperitoneum treatment.

(ii) *Disease not controlled by P.P.* In 39 patients, the clinical course was such that their lesions were not adequately controlled by P.P. Usually cavitation persisted or even became more marked, or consolidation did not resolve. In only a few was there bronchogenic spread. In nearly half, the P.P. helped in regression of lesions, so that more efficient methods of treatment could be employed. In the remainder, however, disease was very frequently aggravated and patients had to be salvaged, particularly by the surgical procedures mentioned below. Pneumoperitoneum was maintained for an average of seventeen months.

The varying success of the subsequent measures used is shown in the following table:

Measure	*No.*	*Alive and well*	*Invalid*	*Dead*
Artificial pneumothorax	15*	8	2	1
Extrapleural pneumothorax ..	2	2	0	0
Thoracoplasty	23	16	3	4
Resection	2	2	0	0

* 4 had subsequent thoracoplasties.

(iii) *Bronchogenic spread following P.P.* Spread is defined here as the abrupt appearance of infiltration in areas of one or both lungs which had previously been spared, or where there had been only the lightest involvement which had now suddenly and greatly increased.

In 36 patients there was such spread following closely the onset of lobar collapse. Thirty (83 per cent.) of these patients had died, 5 (14 per cent.) were alive and well and 1 was invalid, by the beginning of 1954.

Lobar collapse was the prime cause of bronchogenic spread in these cases. This is shown by three points:

(*a*) Atelectasis and spread both occurred after a mean two months had elapsed since the induction of the pneumoperitoneum—*i.e.*, at approximately the same time.

(*b*) The mean estimated duration of disease *before* pneumoperitoneum induction in this group was 11·4 months, during which time massive spread might well have taken place. In fact, it did not, in almost all of these cases, but erupted two months (mean) *after* induction.

(*c*) A comparable type of spread may be found among the control (non-collapsed) cases by taking those who died and in whom spread must have taken place before death. These cases are comparable to the "collapsed" cases in their fate because 83 per cent. of the latter died. In these "non-collapsed" cases, the mean interval between pneumoperitoneum induction and spread was ten months as against two months with the latter; therefore some peculiar factor must have been present in the "collapsed" cases to account for this wide difference in time-relationships. This was almost certainly the occurrence of lobar atelectasis.

Clinically, in very many of these patients their lesions were regressing favourably on bed rest, and it was only after the induction of pneumoperitoneum that their condition was rapidly and disastrously reversed. Unfortunately, there were no obvious features by which these patients could be distinguished from those whom pneumoperitoneum helped (Group i), *before* the induction of pneumoperitoneum. Lastly, in a very much smaller number of patients their disease had advanced steadily since diagnosis and the use of pneumoperitoneum only hastened their inevitable death.

Persistence of Cavitation in Relation to Spread

In nearly a third of this whole group, cavities were not present at the time of spread, as is shown below. Spread, therefore, may arise both from cavitated and non-cavitated atelectatic lobes, distal dammed-up material being released through the occasional reopening of blocked bronchi, particularly during coughing (Wilson, 1945).

Type of disease	*No.*	*Dead*	*Alive*
Cavity persisted	25	22	3
Previous cavity closed by this time	8	6	2
Cavity always absent	3	2	1

(iv) *Relapse after the Premature Abandonment of Pneumoperitoneum.* In 10 patients their cavities disappeared and their lesions were resolving satisfactorily. Unfortunately, their pneumoperitoneum was abandoned after a mean 1·9 years and within a mean two months (varying from one to five months) massive spread occurred in all and cavities reopened in 4. This is particularly striking in that such spread had not occurred either during the mean seven months before their pneumoperitoneum was induced nor during the mean 1·9 years that this latter treatment was continued. It is clear that the premature abandonment of the pneumoperitoneum was the main factor in these patients' relapse, particularly when they are compared to group (i). By the beginning of 1954, 6 had died, 3 were invalid and 1 was well.

Retrospect

Two-fifths of all the patients had died, while another fifth were still invalid by the beginning of 1954, six and half to ten years after the date of pneumoperitoneum induction. Exudative disease, which comprised the original lesions of nearly all, is consequently by no means one of the optimal indications for

pneumoperitoneum therapy that it has been universally held to be. Bed rest and posture, followed by thoracoplasty at a suitable time, would certainly have saved a far larger number of these patients (Thomas, 1948; Mitchell, 1955).

Chemotherapy has, it will be obvious, greatly diminished the incidence of atelectasis and of its unfortunate sequelæ. Nevertheless, I have seen many examples of collapse, of spread and of relapse complicating pneumoperitoneum therapy, despite the use of the anti-tuberculous drugs. Though these disasters can often be retrieved by chemotherapy, they should be watched for and guarded against even in contemporary treatment. It is wise, if the use of pneumoperitoneum is contemplated, to treat exudative lesions by several months of chemotherapy before induction; this will usually, but not invariably, remove the paramount dangers of collapse and of spread. Similarly, if pneumoperitoneum is used as definitive treatment, it should be maintained for four years or more, to obviate relapse.

Conclusions and Summary

Lobar collapse complicating pneumoperitoneum treatment is common, particularly in exudative disease. It is a grave phenomenon, its principal danger being bronchogenic spread, of which it is the prime cause and which was for the most part fatal in the series studied.

Various features bearing on its ætiology and prognosis have been analysed.

Despite chemotherapy, collapse and its accompanying dangers may still occur.

(1) This paper summarises part of a thesis accepted for the degree of M.D., University of Cambridge.

(2) I am grateful to Dr. L. E. Houghton and Dr. K. R. Stokes of Harefield Hospital for access to records and for the former's criticism. I am also grateful to Dr. E. H. Hudson, Dr. J. Smart and Mr. J. R. Belcher of the London Chest Hospital for their advice.

(3) I am particularly indebted to Dr. B. Benjamin for his statistical advice and approval of results.

REFERENCES

Banyai, A. L. (1946): " Pneumoperitoneum Treatment," London, ch. 10, p. 124.
Bobrowitz, I. D. (1953): *Dis. Chest*, **24,** 82.
Brinkman, G. L. (1953): *Brit. J. Tuberc., Dis. Chest*, **47,** 131.
Brooks, W. D. W. (1948): *Brompton Hosp. Rep.*, **7,** 51.
Bishop, P. W. (1946): in " Clinical Radiology," U.S., vol. 1, ch. 17, p. 319.
Coello, A. J., and Nagley, M. N. (1948): *Tubercle (Lond.)*, **29,** 231.
Coello, A. J. (1951): *J. thorac. Surg.*, **21,** 135.
Coope, R. (1948): " Diseases of the Chest," Edinburgh, ch. 7, p. 93 *et seq.*
Coryllos, P. N. (1933): *Amer. Rev. Tuber.*, **28,** 1.
Coryllos, P. N. (1936): *Amer. Rev. Tuberc.*, **33,** 639.
Crow, H. E., and Whelchel, F. L. (1945): *Amer. Rev. Tuberc.*, **5,** 367.
Cuthbert, J., and Nagley, M. M. (1948): *Tubercle (Lond.)*, **29,** 154.
David, J. D. D. (1954): *Tubercle*, **35,** 90.
Dunham, K. (1917): *Amer. Rev. Tuberc.*, **1,** 489.
Eloesser, L. (1937): *J. Thorac. Surg.*, **7,** 1.
Erwin, G. S. (1939): *Brompton Hospital Rep.*, **8,** 43.
Farquharson, M. (1950): M.D. Thesis, Cambridge University.
Farquharson, M. (1951): *Tubercle (Lond.)*, **32,** 108.
Fegiz, G. (1946): *Ann. Ist. Forlanini*, **13,** 169.
Foster-Carter *et al.* (1952): *Brompton Hosp. Rep.*, **21,** 3.
Fox, W. (1950): *Thorax*, **5,** 183.

GLENN, E. E. (1931): *Amer. Rev. Tuberc.*, **23,** 507.
GOLDEN, R. (1941): " Diagnostic Roentgenology," New York, vol. 1, ch. 3, p. 84.
HABLISTON, C. C. (1928): *Amer. J. Sci.*, **185,** 830.
HENNELL, H. (1931): *Amer. Rev. Tuberc.*, **23,** 461.
HIMALSTEIN, M. R. (1951): *Dis. Chest.*, **19,** 346.
HOUGHTON, L. E. (1950) *Tubercle (Lond.)*, **31,** 50.
ITTURRIAGA, A. P. (1942): *Rev. clin. esp.*, **5,** 56.
JONES, R. S., and ALLEY, F. H. (1951): *Amer. Rev. Tuberc.*, **63,** 381.
KERLEY, P., and TWINING, E. W. (1951) in " X-ray Diagnosis," London, vol. 2, p. 319.
LACHANCE, R. (1952): *Un. Méd. Can.*, **81,** 170.
LOESCHCKE, H. (1938): *Beitr. Klin. Tuberc.*, **68,** 251.
MACDONALD, A. W. B. (1952): *Tubercle (Lond.)*, **33,** 194.
MAHER-LOUGHNAN, G. P. (1950): *Tubercle (Lond.)*, **31,** 74.
MELLIES, C. J. (1939): *J. Miss. med. Ass.*, **36,** 430.
MITCHELL, R. S. (1951): *Amer. Rev. Tuberc.*, **64,** 1.
MITCHELL, R. S. (1955): *Amer. Rev. Tuberc.*, **72,** 487 and 502.
National Tuberc. Ass. of America (1950): " Diagnostic Standards," New York.
PACKARD, E. N. (1928): *Amer. Rev. Tuberc.*, **18,** 7.
PAGEL, W. and SIMMONDS, F. A. H. (1939): *Amer. J. med. Sci.*, **197,** 281.
PAGEL, W. and SIMMONDS, F. A. H. (1942): *Amer. J. med. Sci.*, **203,** 177.
PINES, A. (1954): *Tubercle (Lond.)*, **33,** 72.
PINES, A. (1956): M.D. Thesis, Cambridge University.
PINNER, M. (1937): in " The Collapse Therapy of Pulmonary Tuberculosis," London, ch. 4, p. 69.
RAFFERTY, R. N. (1943): *J. thorac. Surg.*, **12,** 578.
Registrar-General's Statistical Review of England and Wales, London, 1944-47.
SADLER, R. L. (1954): *Brit. med. J.*, **1,** 359.
SALKIN, D. (1936): *Tubercle (Lond.)*, **18,** 71.
SCADDING, F. *et al.* (1952): *Brompton Hosp. Rep.*, **21,** 104.
STOKES, J. B. (1938), *Illinois med. J.*, **73,** 137.
SWEANEY, H. *et al.* (1931): *Amer. Rev. Tuberc.*, **24,** 554.
TEMPLE, L. J. (1955): *Thorax*, **10,** 220.
THOMAS, D. M. E. (1948): *Tubercle (Lond.)*, **29,** 216.
WILLIAMS, E. L. (1951): *Tubercle (Lond.)*, **32,** 26.
WILSON, N. J. (1954): *Dis. Chest*, **11,** 36.

CERASE

A WAX-DECOMPOSING ENZYME IN EXPERIMENTAL TUBERCULOSIS

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It is well known that leucocytes and other cells of the reticulo-endothelial system contain a variety of enzymes which attack the cellular structures of dead or living microbial agents. Among known enzymes one, lysozyme, causes the lysis of certain living bacteria, probably by attacking a structural component of their cell wall. There are many reports also describing the existence in leucocytic extracts of fractions other than lysozyme which possess a direct bactericidal activity. Among these are the hæm compounds. It has long been known that hæms possess antibacterial activity in the free state, but this is not so when they are combined with proteins. It is worth noting that the pigment of green pus is due to the presence in leucocytes of very high concentrations of a hæm-containing enzyme, verdoperoxidase. Contact between enzyme and substrate—in this case a living microbe—occurs naturally on the surface of the latter, that is to say, on its capsule or cell-membrane. Absorptive affinity and enzyme specificity towards cell-wall components are important factors in determining the bactericidal power of the enzyme, so that its absence may contribute to the development of a systemic infectious disease—*e.g.*, when bacteria can multiply within the cells, as in leprosy (Metchnikoff, 1893) and tuberculosis (Mackaness, 1954), or when they are carried about by the cells.

Resistance of both kinds of mycobacteria seems to be associated with their acid-fastness. In 1942 Rosenblatt, Fullar and Gessler observed the cell-wall of mycobacteria under an electron microscope (30,000 × magnified). It appears to have a uniform granular structure. Investigations into the chemical composition of the lipids of mycobacterial cell walls have been in progress for many years, and various workers have shown them to be mixtures of different esters and free long-chain fatty acids, such as phthioceric acid, phthioic acid, tuberculostearic acid, mycocerosic acid, mycolic acid isomers, etc. (Stodola and Anderson, 1936; Anderson, Stodola and Lesuk, 1938; Velick, 1944; Ginger and Anderson, 1945; and Chanley and Polgar, 1950). This presupposes a waxy compound, so that the acid-fast membrane must be a fine waxy emulsion of high viscosity. It is well known that waxes are nearly always physiologically inert, so that their rôle is mostly protective in spite of their high caloric value. In mycobacteria they form the protective material in the cell-wall and are responsible for its acid-fastness.

Vertebrata are unable to decompose waxes either intracellularly or in the digestive apparatus, but at the beginning of this century, Metalnikov (1906)

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demonstrated the existence of wax-decomposing enzymes in wax-moth larvæ (*Galleria melonella*). The larvæ of this insect live entirely on beeswax. Metalnikov (1914) discovered further that *Mycobacterium tuberculosis* and *Mycobacterium lepræ* can be digested very quickly by the leucocytes and other cells of these larvæ, and that in their digestive tract bacteriolysis is accelerated. By administration of extracts of the larvæ, he succeeded in keeping tuberculous guinea pigs alive for as long as a year after the death of the last control animal. Muftic (1949) obtained a crystalline wax-decomposing enzyme from a yeast-like fungus (*Blastomyces cerolytica*) which derives its energy from wax, and described its bactericidal activity against different saprophytic and pathogenic mycobacteria. Mankiewicz (1952) obtained an active enzyme from an acetone precipitate of wax-moth larval extracts, which protected guinea pigs against 2 LD of tubercle bacilli ($H_{37}R_v$). Kuzniecow and Wojciechowsky by means of different buffers also prepared an enzyme solution from an extract of larvæ of the wax-moth. This showed a strong bactericidal action against *Mycobacterium tuberculosis*.

For all enzymes which decompose waxes and wax-like substances Metalnikov's designation (1906) " cerase " has been adopted. The properties of the enzyme isolated by Muftic (1955) are described in several papers. Its composition is that of a cyclophoras-peroxidase of long carbohydrate chains, containing organic compounds of iron but not hæms. Its peroxidase action is utilised for titrating its potency (measured in units), and its purity is estimated by determination of the iron content per gramme of substance. Like many enzymes containing heavy metals, cerase is thermolabile, and for this reason sterile solutions of the enzyme can be prepared only by filtration through a bacteriological filter. Cerase was not found to exert any bacteriostatic or bactericidal effect on other microbes than acid-fast ones.

In this paper we propose to describe the action of cerase in experimental tuberculosis in guinea pigs. The number of animals was limited by the small quantity of cerase available, and future experiments will be carried out on a larger scale.

Materials

1. Fifty guinea pigs (male and female) weighing initially between 280-400 gm.

2. *Mycobacterium tuberculosis hominis*—$H_{37}R_v$, obtained by courtesy of the Bacteriological Institute, Cairo University, and from the National Collection of Type Cultures, Medical Research Council of England. They were cultivated in Dubos' liquid medium, and before use re-inoculated on Loewenstein-Jensen's medium.

3. Cerase (wax-decomposing enzyme) solutions in ampoules containing 50 mg. of crystalline enzyme per ml. The enzyme was obtained in A.M.A. Laboratories Ltd. (Cairo, Heliopolis) by extraction from surface cultures of *Blastomyces cerolytica* by a special procedure described by Muftic (1955). The sterility of the ampoules was confirmed by several sub-cultures, and the activity of the enzyme estimated from its peroxidase value in an emulsion of ceryl-cerotate.

Methods

All animals were inoculated intraperitoneally with 1 mg. (moist weight) of tubercle bacilli ($H_{37}R_v$). The extreme virulence of the infection was shown by the fact that the first of twenty-five untreated animals died nineteen days after being inoculated, while the last died two months after inoculation.

Cerase was administered to a second group of twenty-five guinea pigs. The administration was begun two weeks after inoculation of the animals with *M. tuberculosis*. About 50 mg. of cerase per kg. of body weight was injected intramuscularly every fourth day for ten weeks. Each of the treated animals received a total of approximately 0·5 g. of cerase. Three of the treated animals died 7, 9 and 12 weeks respectively after inoculation; five animals were killed 6, 9, 12, 14 and 20 weeks after inoculation, and the remaining animals treated by cerase were electrocuted on the 210th day.

Histopathological Findings

Lungs

The most striking feature observed in the lungs of the first animal to be killed after cerase treatment was the paucity of giant cells in the tuberculous lesions, in comparison with the control animals. The cells were small, with two to five nuclei. Occasionally, the tubercles were composed of an agglomeration of epithelioid cells occupying two or three alveoli. Ziehl-Neelsen's stain showed very few acid-fast bacilli in some tubercles.

For 6-12 weeks two types of lesion were distinguishable, namely, tubercles composed of epithelioid cells occupying one or many alveoli and lymphocytic islands composed of 20-40 lymphocytes. Very few giant cells were seen. The peribronchial lymph nodules were considerably swollen.

From 12-20 weeks there was a remarkable reduction in the number of foci to about one-sixth of the previous amount, and the histological picture they showed was most unusual. The inter-alveolar septa were apparently normal, but in the alveolar cavities many oval cells with multiple nuclei were seen. Although there was no proliferative tuberculosis this appearance may indicate the presence of desquamative alveolitis.

Thirty weeks after inoculation, in the treated animals, there was no sign of the pathological changes previously described. The lung tissue sections were absolutely normal.

It seems, therefore, that in the course of some 200 days the tuberculous process increased, then diminished and finally healed entirely without caseation being seen at any time. Acid-fast bacilli became increasingly rare until they disappeared after the twelfth week. The lungs of the last group of treated animals to be killed could not be distinguished from the lungs of an uninfected animal and it is difficult to believe that 200 days previously these animals had received 1 mg. of virulent tubercle bacilli intraperitoneally.

Liver

In the first six weeks there was occasional tubercle formation with many polynuclear and mononuclear leucocytes. There were a few emboli. Giant cells were few but large, with more than 20 nuclei, and surrounded by lympho-

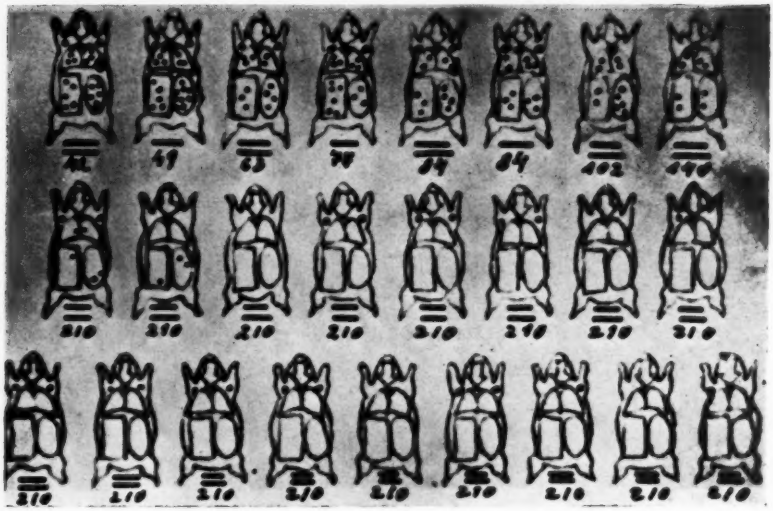

FIG. 1.—Schematic representation of the extent of tuberculosis observed at necropsy in tuberculous guinea pigs, infected by intra-peritoneal inoculation with one milligramme (moist weight) of *Mycobacterium tuberculosis* ($H_{37}R_v$). The animals were treated by intramuscular injection of cerase (50 milligrammes per kilogramme of body weight) every fourth day. A single black bar below an animal indicates that it died prematurely. A double black bar indicates that the animal was killed. The number below the bar indicates the number of days after inoculation with tubercle bacilli until death of the animal.

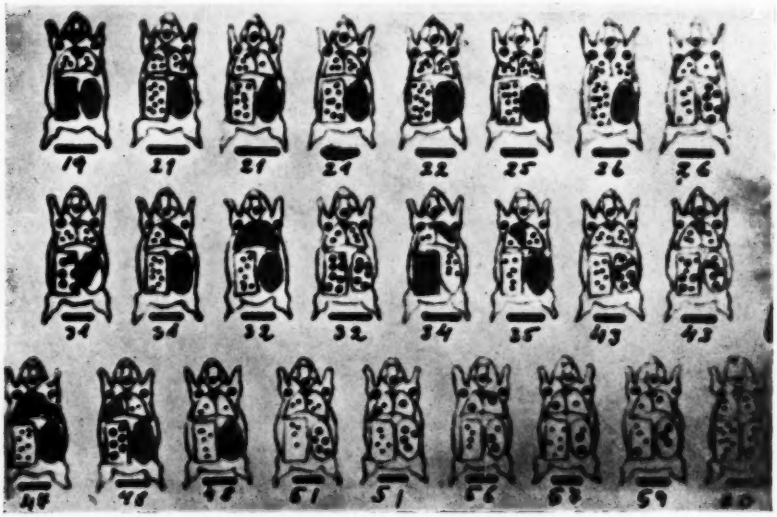

FIG. 2.—Schematic representation of the extent of tuberculosis observed at necropsy in tuberculous guinea pigs, infected by intraperitoneal inoculation with one milligramme (moist weight) of *Mycobacterium tuberculosis* ($H_{37}R_v$). The animals were not treated and served as controls. A single black bar below an animal indicates that it died prematurely. The number below the bar indicates the number of days after inoculation with tubercle bacilli until death of the animal.

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cytes. Plasma cells were also found. Fourteen weeks after inoculation there was considerable lymphocytic infiltration, but for the succeeding 20 weeks tubercles were extremely rare, and there was no evidence of change in the hepatic parenchyma.

Spleen

In the initial 6-8 weeks there were many small giant cells in the sinuses as well as groups of epithelial cells in the lymphoid follicles. After 14 weeks a remarkable change was seen, all the sinuses being engorged with small giant cells. Twenty to thirty weeks after inoculation, however, there were no epithelial cells left in the lymphoid follicles, and the sinuses looked normal.

Conclusion

It is evident that the lesions of these tuberculous guinea pigs, treated by wax-decomposing enzymes—cerase—did not show any tendency to caseation, and histological healing had occurred in about 140 days. Figs. 1 and 2 illustrate the course of the disease in the twenty-five guinea pigs treated with cerase, and the twenty-five control animals. Three animals died during treatment as a result of Pasteurella infection.

Intramuscular injection of cerase has no necrotic action on surrounding tissue, nor were any pathological changes seen affecting the kidney, heart or central nervous system. The first three injections caused a rise of temperature to 41·5° C. (p.r.), but following the next dose it did not reach 40° C. Normal, non-infected animals when injected with cerase did not show any rise in temperature. So far as we can determine cerase is not excreted by the kidney, but is destroyed in the organism or eliminated in some other way. Peroxidasic activity of the serum of treated animals was observed for five weeks after the last injection of enzyme.

Clearly these results must be enlarged upon by more extensive investigations, as a group of only twenty-five animals, the largest permitted by the amount of enzyme available, is too small to permit any definite conclusions being drawn regarding the pharmacological and toxicological behaviour of the enzyme preparation. I hope, however, that in the future it will be possible to study these problems on a large scale.

Discussion

Treatment of tuberculosis by lipolytic enzymes was introduced first by Fiessenger and Marie (1904). The enzymes they used were obtained from lymphatic glands of tuberculous animals. Later Fiessenger, Gajdos and Pezzangora (1935) used heptic lipase, and lipo-oxidase in tuberculous guinea pigs. They succeeded in reducing the number of foci. Corper and Sweany (1918) observed autolysis of *Mycobacterium tuberculosis* after its decapsulation by organic solvents. Recently, Prina (1952) found that streptomycin possesses a lipolytic action for tributyrin, tweens and lipids from tubercle bacilli. Mankiewicz (1952) found that cerase from larvæ of *Galleria melonella* abolishes the acid-fastness of mycobacteria, coincidentally changing their cytochemical properties so that they become negative in the Dubos neutral red reaction, and

retain no Sudan Black "B" after treatment with acetone. Muftic (1955) detected the formation of fat peroxides in *Mycobacterium tuberculosis* after treatment with very dilute cerase solutions. The protective action of cerase in tuberculous guinea pigs was observed by Metalnikov (1920) and Mankiewicz (1952). In our experiments the disease was better controlled by purified and highly concentrated preparations and using greater amounts of enzyme than did these two authors. It seems that peroxide (fat) formation and decomposition of waxy substances of the cell wall of mycobacteria prevents caseation in infected animals, possibly because of changes in the antigenic structure of the bacilli. The enhanced lymphocytosis seems to be related to the benign advancement of the infection. The small number of giant cells suggests that there is little stimulus to the reticulo-endothelial system to attack the germs, which are already undergoing lysis. This is the same picture that Metalnikov (1906) observed fifty years ago in the tissues of larvæ of *Galleria mellonella* infected with tubercle bacilli.

Giant cell formation, caseation, deposition of fibrin and collagen at the site of the lesion appears to be the tissue response to invasion where tissue enzymes are incapable of destroying the invader. This incapability arises partly because the invader is protected by resistant material, which cannot be decomposed by the enzymes available in the tissues, and partly because the invader secretes substances which inhibit the enzymes. The former explanation applies in the case of acid-fast microbes. Members of the Vertebrata cannot digest wax-like substances, and the absence of wax-destroying enzymes permits the complicated tissue reactions to tuberculous infections. The problems of infection and immunity are less complex than some theories suggest. It is a question of a biological fight between host and invader, where both are substrates and both enzyme producers; the end result is digestion of one of them.

Summary

Guinea pigs infected intraperitoneally by *Mycobacterium tuberculosis hominis* ($H_{37}T_v$) were treated with wax-decomposing enzymes—"cerase." The course of the disease was changed and no caseation was observed. About 200 days after infection the treated animals showed histological healing of lesions. The suppression of infection was striking when compared with control animals which died between 19 and 60 days after inoculation. The total dose of cerase for one animal was about 0·5 gm. Cerase is an iron-peroxidase; its activity can be demonstrated in the serum for several weeks after injection. There was no evidence of excretion of the enzyme by the kidney. The bactericidal action of the cerase is due probably to its power in decomposing the waxy membrane of mycobacteria, which the tissues of organisms of the Vertebrata cannot do.

One part of this research was done in A.M.A. Laboratories Ltd. (Heliopolis, Cairo) at the instigation of Dr. Z. Madgachian, director. The other part was facilitated by the help of the Iraqian Ministry of Public Health.

Some necessary material was given by the Rockefeller Foundation in Cairo by courtesy of Dr. W. MacIntosh. The strains of *Mycobacterium tuberculosis* were obtained from Prof. M. Gohar of the Bacteriological Institute, Cairo University, and from the National Collection of Type Cultures, Medical Research Council of England.

To all of them we extend our grateful thanks.

REFERENCES

ANDERSON, R. J., STODOLA, F. H., and LESUK, A. (1938): *J. biol. Chem.*, **126,** 505.
CHANLEY, J. D., and POLGAR, N. (1950): *Nature*, **166,** 639.
CORPER, M. C., and SWEANY, S. (1918): *J. Bac.*, **3,** 129.
FIESSENGER, N., and MARIE, P. L. (1904): *C.R. Soc. Biol. (Paris)*, **67,** 107.
FIESSENGER, N., GAJDOS, A., and PEZZANGORA, F. (1935), *C.R. Soc. Biol. (Paris)*, **120,** 985.
GINGER, L. G., and ANDERSON, R. J. (1945): *J. biol. Chem.*, **157,** 203.
KUZNIECOW, A., and WOJCIECHOWSKY, E. (1950): *Med. dośw. Mikrobiol.*, **2,** 245.
MACKANESS, G. B. (1954): *Amer. Rev. Tuberc.*, **69,** 479.
MANKIEWICZ, E. (1952): *Canad. J. med. Sci.*, **30,** 116.
METALNIKOV, S. (1906): *Arch. scien. biol. de Petersburg*, **12,** 300.
METALNIKOV, S. (1914): *Z. ImmunForsch.*, **22,** 235.
METALNIKOV, S. (1920): *Ann. Inst. Past.*, **34,** 810.
METCHNIKOFF, E. (1893): Lectures on comparative Pathology of Inflammation, London.
MUFTIC, M. (1949): *Experientia (Basel)*, **7,** 219.
MUFTIC, M. (1955): *Enzymologia (Amst.)*, BE 339.
MUFTIC, M. (1955): *Enzymologia (Amst.)*, Vol. XVII, Fasc. 4.
PRINA, C. (1952): *Boll. Soc. ital. biol. sper.*, **28,** 1502.
ROSENBLATT, M. B., FULLAR, E. F., and GESSLER, E. (1942): *Amer. Rev. Tuberc.*, **46,** 587.
STODOLA, F. H., and ANDERSON, R. J. (1936): *J. biol. Chem.*, **114,** 467.
VELICK, S. F. (1944): *J. biol. Chem.*, **154,** 497.

TUBERCULOSIS OF EMPHYSEMATOUS BULLÆ

By B. Golberg

From the Ashford Chest Clinic, Ashford Hospital, Middlesex

Infection of pre-existing emphysematous bullæ in the lungs is an uncommon occurrence, considering the frequency with which bullous changes are found in chest X-rays. In the few cases so far described, those of Rigler (1946), Weisel and Slotnick (1950), and two of Rothstein's series (1954) showed infection of non-tuberculous nature. In the eight other cases described by Rothstein the bullæ had been invaded by tuberculous disease. The case to be described here has many features in common with these eight cases, but differs in its outcome.

A 71-year-old-male was first seen at the Ashford Chest Clinic on May 2, 1955. He gave a history of cough with sputum and wheezing for many years, worse in the winter, and shortness of breath for the past two years. The shortness of breath had been much worse for the past three weeks. He said he had had "heart trouble" in the first World War, and had been worried about his health ever since.

On physical examination chest movements were poor but equal, and breath sounds over both lungs were diminished. No abnormalities were found in the cardiovascular system, apart from a blood pressure of 170/110. Other systems were essentially normal.

Chest X-ray showed marked emphysematous changes in both lungs, localised largely to the upper and mid-zones, with bullous changes more obvious on the left than on the right. Two calcified foci were present in the right upper zone, and there was also a little mottling and streaking at the upper pole of the right hilum. (Fig. 1.)

A diagnosis of emphysema was made, and symptomatic treatment prescribed. He continued to complain of increasing cough and shortness of breath but managed to carry on with his restricted activities until the end of December, when he became acutely ill with a bronchopneumonia.

Hospital Admission

The patient was admitted to the medical wards of the Ashford General Hospital on January 1, 1956, as an acute emergency in a confused state. Relatives provided the history that he had had an unproductive cough for the past two or three months, and had been on liquid foods only for the past two weeks (? because of difficulty in swallowing). He had been treated with penicillin for the previous two days, without improvement.

On examination the patient was pale and emaciated, and confused. Temperature was 100·4, pulse 104, respiration 23, blood pressure 150/110. The left lower chest was dull to percussion and numerous râles were audible anteriorly.

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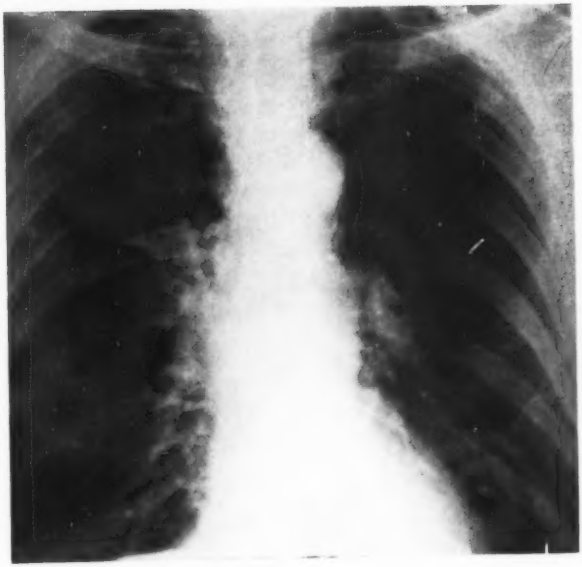

FIG. 1.—Clinic film 2.5.55 showing bullous emphysema.

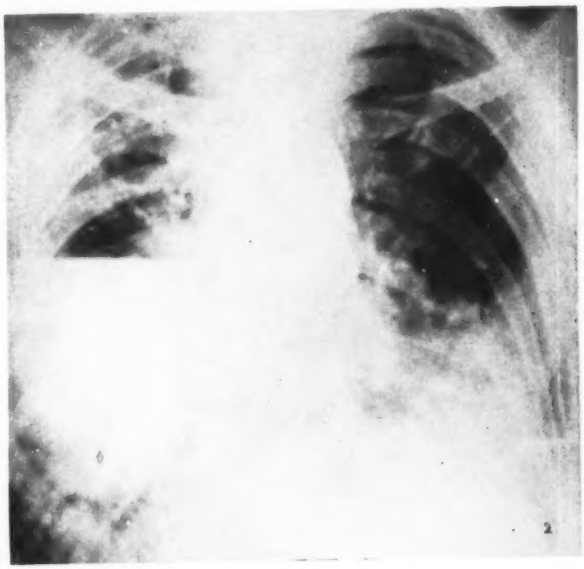

FIG. 2.—Hospital film 1.1.56 showing extensive superimposed tuberculous disease.

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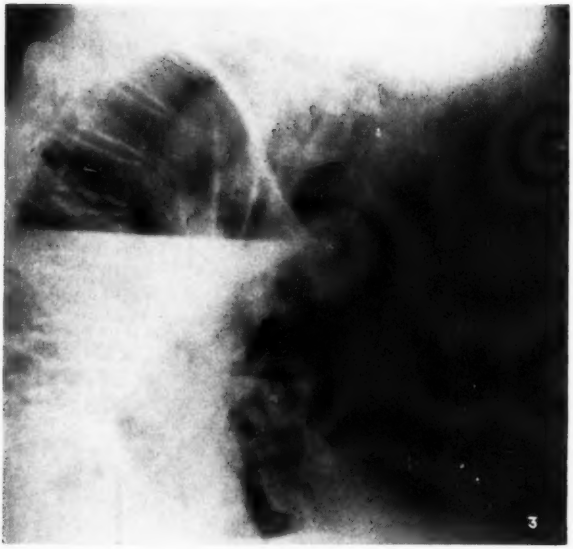

FIG. 3.—Right lateral film showing location of the fluid levels.

X-ray of chest revealed a bizarre picture. Coarse mottling was present in the right upper and lower zones, and irregular consolidation in the left lower zone. A fair quantity of fluid was present in the right midzone, with a fluid level, and also a smaller fluid level noted in the left lower zone. In addition both upper zones were emphysematous. (Fig. 2.)

A right lateral film showed the fluid on the right to be lying posteriorly, in a triangular space bounded above by the thickened and elevated greater fissure, posteriorly by the chest wall, and below by consolidated lung tissue. The small amount of fluid on the left was seen to lie centrally. (Fig. 3.)

A presumptive diagnosis of pyopneumothorax was made, and the right chest aspirated. Loculated purulent fluid was obtained and penicillin introduced.

Investigations

Blood count: Hæmoglobin 10·1 g.
Leucocytes 15,200; Polymorphonuclears 82 per cent. Lymphocytes 18 per cent.
Blood urea 60 mg.
Pus from chest: No organisms seen on Gram staining; many acid-fast bacilli on Ziehl-Nielson staining.
Culture: Heavy growth of typical tubercle colonies.
Sputum: Strongly positive for acid-fast bacilli.

Progress

The patient was transferred to the tuberculosis wards in view of these findings, where his condition continued to deteriorate rapidly. He died on January 11, 1956. Permission for autopsy was not obtained.

Discussion

The appearances on the hospital X-ray films gave rise to considerable discussion while the patient was alive, and a diagnosis of tuberculous bronchopneumonia with bilateral empyemata was considered the most likely. Only after his death was his previous attendance at the clinic discovered. Comparison with these films elucidated the exact nature of the disease. It could be seen that the original large emphysematous bullous spaces had become infected by extension of tuberculous disease—probably already present in the right hilar area in the earlier film.

Rothstein (1952, 1954) has described the radiological appearances in these cases as complicated and unusual, or even bizarre. The tuberculous infiltration extends into bullar septa, or lung tissue surrounding the bullae, and gives rise to appearances simulating extensive caseous pneumonia which has undergone breakdown. The same pathological features would account for the X-ray appearances here.

Fluid levels, present in the bullæ on both sides here, were found in six instances in his first five cases. It is interesting to note his experience that in almost every instance where a fluid level occurred in a bulla, the bulla gradually shrank and disappeared, leaving at most a linear shadow suggesting fibrosis.

The pre-existing emphysematous changes in this case differ from those previously described by their very extensive degree. They had already resulted in gross diminution in respiratory reserve when the patient was first seen, and before tuberculous infection had taken place to any extent. Superimposed tuberculosis reduced the remaining function drastically. His advanced age and poor general condition on admission helped to decide the outcome.

Summary

A case of tuberculous infection of extensive emphysematous bullæ is described. The X-ray appearances were difficult to interpret until a film prior to infection was found for comparison. The fatal outcome in this case is in contrast to the good prognosis in the eight other cases described by Rothstein, and is ascribed to the extensive original bullous changes, advanced age and poor general condition.

I wish to thank Dr. P. E. Baldry for permission to publish this case.

REFERENCES

Rigler, L. G. (1946): "The Chest." Chicago, Ill. Year Book Publishers. 1946, p. 168.
Rothstein, E., and Moberley, J. W. (1952): *Dis. Chest*, **22**, 587.
Rothstein, E. (1954): *Amer. Rev. Tuberc.*, **69**, 287.
Weisel, W., and Slotnick, I. (1950): *Amer. Rev. Tuberc.*, **61**, 742.

HODGKIN'S DISEASE AND CASEOUS TUBERCULOSIS

(WITH REPORT OF A CASE)

By E. H. Horton

From Glan Ely Hospital, Cardiff

Hodgkin's disease has long been recognised to have a close association with tuberculosis, although its ætiology still remains imperfectly understood. It has often been considered to be a result of infection with the tubercle bacillus and some cases have ultimately developed miliary tuberculosis. Ewing (1940) records the frequent presence of tuberculous stigmata in Hodgkin's disease and quotes a case of pulmonary tuberculosis in which, in three small adjoining bronchial lymph nodes, he found miliary tubercles in one, a diffuse lymphocyte response in another, and typical Hodgkin's granuloma in the third. He also records the production of tuberculosis in guinea pigs by inoculation of Hodgkin's tissue, but considers the absence of stainable bacilli in these lesions to be a deficiency in the evidence that Hodgkin's disease is tuberculous in origin.

Case Reports

The patient, a female of 56 years, was first seen in December 1953, when she had enlargement of the left supra-clavicular lymph nodes. One of these was excised and sent for biopsy; it was reported as showing caseous tuberculosis. She was treated with streptomycin and iso-nicotinic acid hydrazide, but failed to improve and soon became wasted and anæmic. She also had symptoms of an abdominal nature and fairly marked enlargement of liver and spleen were noted. Liver function tests were performed and an alkaline phosphatase of 80 + units was found with no other significant changes.

Shortly afterwards, she became jaundiced and œdematous with a total serum protein in the region of 4-5 G./100 ml. Once the jaundice was established, the alkaline phosphatase fell to a level of approximately 20 units. Bile and urobilinogen were identified in her urine. She died in March 1954.

Extract from Post-mortem Examination Report

(Dr. J. G. Leopold, Welsh National School of Medicine)

" Deeply jaundiced; no peripheral œdema."

There were enlarged and fleshy glands on the left side of the neck.

Gastro-Intestinal Tract

The liver was enlarged and the cut surface showed fine infiltration. The

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bile ducts were patent and the gall bladder, apart from a few soft concretions, was normal. The pancreas showed no tumour.

Hæmopoietic System

The spleen was enlarged and soft with small pale areas scattered through its substance. In the abdomen there were grossly enlarged glands, the architecture of which had been destroyed.

Microscopic Examinations

Biopsy of Gland of Neck: Caseous tuberculosis.

Spleen: Follicular deposits of Hodgkin's tissue.

Mediastinal and Cervical Lymph Nodes: Hodgkin's disease with much necrosis; fibrosis and prominent giant cell formation.

Liver: Centrilobular necrosis with slight Hodgkin infiltration of the portal tracts.

Sternal Marrow: Normally cellular, but an intense eosinophilia with a paucity of normoblast cells, but no evidence of Hodgkin's disease.

Discussion

Diagnosis of Hodgkin's disease was not made in this case until death had occurred. It had, of course, been considered in differential diagnosis, but the original discovery of caseous tuberculous lesions in the cervical lymph node biopsy was always the overriding consideration, and the liver enlargement was thought to be tuberculous in nature. Also, the high alkaline phosphatase value recorded at one stage of the illness suggested the possibility of biliary obstruction being caused by enlarged tuberculous glands in the portal fissure.

At post-mortem examination the hepatic enlargement was found to be due to Hodgkin's disease. Furthermore, microscopic examination of the enlarged cervical glands showed the classic pictures of Hodgkin's infiltration on the one hand, and caseous tuberculosis on the other. In fact, different areas of the same gland exhibited this feature. No tubercle bacilli were demonstrated.

This case thus illustrates once more the extremely close relationship that exists between these two conditions. If this had been appreciated more fully, it is felt that the true nature of the condition which ultimately caused death might well have been realised during the course of the illness by further microscopic examination of the cervical glands.

In the light of the clinical course, too much significance was attached to the single biopsy report.

Summary

(1) A case is described presenting with enlarged cervical lymph nodes, biopsy of which revealed caseous tuberculosis. Treatment was with streptomycin and iso-nicotinic acid hydrazide.

(2) Death ultimately occurred from hepatic failure thought to be due to tuberculous involvement of the liver, but subsequently shown to be due to Hodgkin's disease. The features of Hodgkin's disease and caseous tuberculosis were then found to be present microscopically in the same cervical gland.

(3) This case demonstrates once again the close relationship between these two conditions and, in view of the clinical course, Hodgkin's disease might have been considered to be the cause of the fatal illness, despite the original biopsy report.

My thanks are due to Dr. J. G. Leopold of the Welsh National School of Medicine, who performed the pathological examinations, and to Dr. V. Emrys Jones, Medical Superintendent, Glan Ely Hospital, for permission to publish the case.

REFERENCES

EWING, J. (1940): "Neoplastic Diseases—a Treatise on Tumours." London: Saunders.
GROSJEAN, A. (1943): *Schweiz. med. Wchnschr.*, **29**, 891.

CORTISONE AND CORTICOTROPHIN FOR TUBERCULOUS PLEURAL EFFUSION

By Mary James

Liverpool Hospital, Frodsham, Cheshire

Cortisone and corticotrophin (ACTH), when used in infections, limit the inflammation, granulation and fibrosis with improvement in symptoms but with the risk of spread of infection (*New England Journal of Medicine*, 1951). Following this, it seemed quite rational that cortisone and corticotrophin could be used with effect in tuberculosis provided they were covered with adequate antimycobacterial therapy.

Le Maistre *et al.* (1951) noted that in seven cases of advanced pulmonary tuberculosis treated with cortisone and corticotrophin there were profound changes in the course of the illness. There was an improved sense of well-being, increased strength and an improvement in appetite. The effect, however, was temporary, lasting only as long as the patients were on hormone therapy.

Linden Walner *et al.* (1952) treated a number of cases of pulmonary and laryngeal tuberculosis with cortisone and corticotrophin. They found that the chest lesions showed some improvement, but the laryngeal lesions were not improved. Biopsy of the laryngeal lesions disclosed an increase in the number of tubercle bacilli, with decrease in the number of tubercles. This exacerbation was due no doubt to the limitation of granulation and fibrosis. The improvement occurring with cortisone and corticotrophin was temporary, patients often retrogressing rapidly after termination of hormone therapy.

Richard Johnson *et al.* (1954) treated thirty-one cases of active pulmonary tuberculosis with combinations of cortisone or corticotrophin and streptomycin. In all cases there were no ill effects, and in many an accelerated improvement of the tuberculous disease, as evidenced by X-ray changes and lowered erythrocyte sedimentation rate.

Houghton (1954) has shown the effectiveness of corticotrophin when combined with the antimycobacterial drugs streptomycin, PAS and isoniazid (INAH) in the treatment of pulmonary tuberculosis. Cortisone being also effective in reducing allergic reactions to PAS and other drugs, it seemed feasible that it could be used to reduce another allergic manifestation, pleural effusion.

A case is described in which corticotrophin and cortisone were used with antimycobacterial cover for the treatment of pleural effusion complicating artificial pneumothorax.

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Case History

Male patient aged 24 years admitted to hospital on 7.3.55 with a diagnosis of pulmonary tuberculosis. His general condition was very good, there being no symptoms.

X-ray 9.3.55: "Unilateral disease with possible left apical cavitation."

Treatment given was enteric coated PAS 16·5 g. daily for four weeks.

X-ray 13.4.55: "Diminished infiltration."

Left artificial pneumothorax was induced on 18.4.55.

X-ray 20.4.55: "L.A.P. with apical adhesion."

Thoracoscopy 12.7.55, all adhesions were successfully cauterised. At the end of the operation 4 oz. clear fluid were aspirated. Post-operatively the treatment was streptomycin 1 g. alternate days; enteric coated PAS 16·5 g. daily and INAH 150 mg. daily for two weeks.

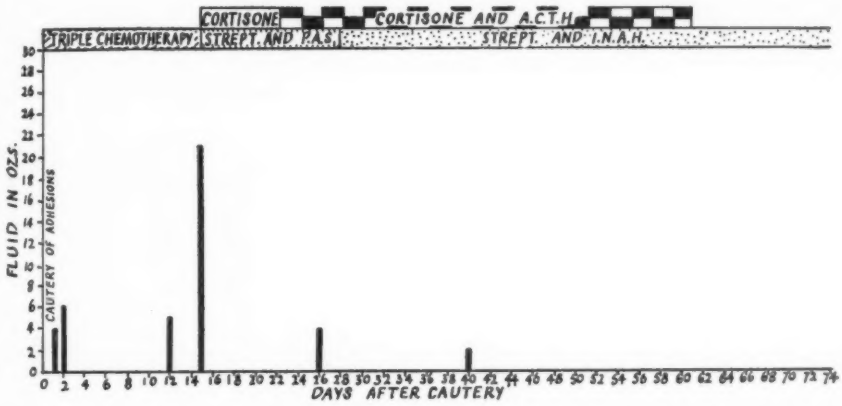


Figure shows acute effusion developing after cauterisation of adhesions, rapidly decreasing when cortisone and corticotrophin were exhibited under antimycobacterial cover.

Fluoroscopy two days after operation disclosed total collapse of the lung and the presence of fluid.

Aspiration: 6 oz. brown fluid.

Fluoroscopy 19.7.55: increased pleural fluid noted.

Aspiration 22.7.55: 5 oz. clear fluid.

Fluoroscopy 23.7.55 showed marked increase in pleural fluid. Clinically this was accompanied by a rise in temperature and pulse rate.

Aspiration 25.7.55: 20 oz. clear fluid.

Two weeks' post-operative chemotherapy now having been completed, the patient was given streptomycin on alternate days with enteric-coated PAS for fourteen days. Cortisone 25 mg. b.d. was exhibited under this cover for seven days.

X-ray 27.7.55: "Left lung fully aerated, no adhesions seen. Fluid present."

Corticotrophin was now alternated with cortisone, commencing with

Aspiration 4.8.55 : 4 oz. clear fluid.

10 units gel twice weekly, Monday and Friday; cortisone being given on Wednesday, Thurday and Sunday.

On 8.8.55 the ACTH was increased to 20 units twice weekly. It was noted,

by means of fluoroscopy, that there was a marked diminution in the rate of formation of pleural fluid.

X-ray 17.8.55: "Pleural fluid slightly above dome of diaphragm."

Aspiration 18.8.55: 2 oz. clear fluid.

The L.AP. was maintained with refills of 400 ml.

X-ray 31.8.55: "Good pneumothorax, with a trace of pleural fluid."

On 2.9.55 the cortisone was reduced to 12·5 mg. b.d., but the ACTH was maintained at 20 units.

On 7.9.55 the ACTH was reduced to 10 units, the cortisone dosage remaining unchanged. After seven days at this level, ACTH and cortisone were discontinued, chemotherapy being continued for a further two weeks.

X-ray 28.9.55 (at the end of course of chemotherapy and hormonal therapy): "Trace only of pleural fluid."

No further aspirations have been necessary.

X-ray 2.11.55 : "Pleural fluid still a trace. Very good pneumothorax."

The patient was discharged on 4.11.55.

Discussion

It has been shown that antimycobacterial therapy has reduced to one-fifth the amount of pleural effusion following cautery of adhesions during artificial pneumothorax treatment. Simultaneously it has eliminated the risk of empyema (Birath, 1953; Erwin, 1954).

In this case an acute effusion developed at the end of a two weeks' course of triple chemotherapy. Cortisone was exhibited under streptomycin and PAS cover; after fourteen days corticotrophin was alternated with cortisone under streptomycin and INAH cover. Under this treatment there was a marked reduction of pleural fluid.

It is known that prolonged administration of cortisone may cause adrenal atrophy. This fact and the shortage of corticotrophin led to the practice of alternating cortisone and corticotrophin. It is probable that more effective economy of corticotrophin could be achieved by giving cortisone for five days, followed by corticotrophin for two days each week.

Topical hydrocortisone has been used for tuberculous effusion by Linquette *et al.* (1954), but it was considered that, in the present case, the known lung lesion pointed to systemic treatment, rather than purely intrapleural therapy.

I wish to express my thanks to Dr. G. S. Erwin for permission to publish this case and for his help in the preparation of it.

REFERENCES

Birath, G. (1953): *Tubercle (Lond.)*, **24,** 260.
Erwin, G. S. (1954): *Tubercle (Lond.)*, **35,** 302.
Houghton, L. E. (1954): *Lancet*, **1,** 595.
Johnson, R., and Davey, W. (1954): *Amer. Rev. Tuber.*, **70,** 623.
Linquette, M., Gondemand, M., and Warot, P. (1954): *Presse Méd.*, **62,** 168.
Le Maistre, C. A., Tompsett, R., Muschenheim, C., Moore, J. A., and McDermott, W. (1951): *J. clin. Invest.*, **30,** 445.
(1951): *New Engl. J. Med.*, **245,** 75. Editorial.
Pickering, G. W. (1952): *Brit. Med. J.*, **1,** 1207.
Walner, L. (1952): *Amer. Rev. Tuber.*, **66,** 161.

REVIEWS OF BOOKS

Thoracic Surgical Management. 2nd Edition. By J. R. BELCHER and I. W. B. GRANT. London: Baillière, Tindall and Cox. 1956. Pp. 228. Illus. 21s.

This excellent book gives a lucid and concise account of the methods of investigation and management of patients before and after thoracic operations. It satisfies a long-felt need by resident surgical staff in thoracic units and its popularity is shown by the early publication of this second edition.

It is essentially practical and gives detailed advice on each procedure, covering the pitfalls which may be encountered and giving an account of the anatomy and mechanics involved wherever necessary. The sections on bronchial anatomy, radiology, artificial pneumothorax and pneumoperitoneum, aspiration of the pleura, bronchography and acute empyema are of more general interest and could be profitably read by all junior medical and surgical hospital staff.

The book is well produced, of a convenient size, and is illustrated with useful diagrams, especially of radiological appearances. The method of presentation of the material in an orderly, tabulated form is ideal for a book of this type and it encourages a methodical way of considering and dealing with problems when they arise.

Chest Clinic Design. Report of the N.A.P.T. Architectural Committee. London and Dunstable: Waterlow and Sons Ltd. 1956. Pp. 108. Illus. 12s. 6d. net.

This companion volume to *Design for Sanatoria* is the report of the N.A.P.T. Architectural Committee on a survey of the objectives in modern Chest Clinic design from the architectural and clinical points of view. The stated aim is to secure safety and convenience to the patient and efficiency to the medical, nursing and administrative staff.

After a brief account of the historical development of the modern chest clinic, the present functions are enumerated and the principles of design outlined. Against this background recommendations are made as to design and layout of the various departments and services either by adapting an existing building or for a new structure. The book is essentially practical and details are given throughout, based on experience and expert advice. Equipment has not been overlooked and necessary items have been listed for the various departments. A number of useful diagrams and plans are included of layouts which are suggested or are actually in operation in various clinics and special suggestions are made for clinics in tropical areas.

There can be no doubt that the volume will prove immensely useful to all those who are concerned with either building a new clinic or modernising or adapting an old one to meet modern requirements.

J. H. PRATT JOHNSON.

Chest Surgery for Nurses. By J. LEIGH COLLIS and L. E. MABBIT. London: Baillière, Tindall and Cox. 1956. Pp. viii+196. Illus. 15s.

This book has now reached its fourth edition; the last one was published five years ago, and this fact alone shows that it fulfils a great need.

The layout follows that in the previous editions, but owing to rapid advances in thoracic surgery and to changes in current teaching, certain sections, notably those on the heart and the œsophagus, have been rewritten.

The anatomical and the physiological aspects of chest disease are well covered, although perhaps a section on the newer methods of assessment of pulmonary function might have been included. The sections which have been brought up to date are excellent, but the impression is given that the remainder of the book has been insufficiently revised. As a result there is still reference to such things as oxygen spectacles in the treatment of anoxia, Tudor Edwards tubes, and open division of adhesions.

Apart from these minor criticisms, there is no doubt that the book will be widely appreciated by nurses in charge of patients with chest disease. It sets out to provide a large number of basic facts upon which the treatment of thoracic cases may be based, and it achieves this purpose admirably.

J. R. BELCHER.

Tuberculosis in the Commonwealth 1955. N.A.P.T. Great Britain: Waterlow and Sons Ltd. Pp. xii+507. Illus. 30s.

This volume gives in full the transactions of the fourth and largest Commonwealth Health and Tuberculosis Conference held by the N.A.P.T. in the Royal Festival Hall in the summer of 1955. In it are to be found short but concise addresses by large numbers of contributors, all experienced in their own particular spheres, on practically every conceivable aspect of tuberculosis. Consideration is given to prevention; child hygiene and infection; differential diagnosis; choice of drugs in medical and surgical treatment; the significance of death-rates; X-ray and tuberculin surveys; tuberculosis in industry; racial problems in tuberculosis; the psychological factor in treatment; tuberculosis and leprosy; mass radiography; care committees and social work generally; the work of sanatorium matrons and nurse-teachers.

It is not to be expected that a book of 500 pages can contain more than a certain proportion of all that can be usefully said on the above subjects, but no reader of this really valuable work can fail to be impressed with the vast amount of sound and reliable information contained in its pages. Much credit is due to the contributors for the way in which they have condensed so many facts into a relatively small space. What makes the reports all the more helpful is the language in which they are presented, so that even the dullest statistics have been made interesting. Thus the volume as a whole is not merely informative as a work of reference; it is also a pleasure to read. We strongly recommend every worker concerned with the problem of tuberculosis (a problem which will be with us for many years to come, despite the dramatic fall in the death-rate) to see that a copy of this book has a place in his or her bookshelf.

MAURICE DAVIDSON.

Chest X-ray Diagnosis. By MAX RITVO. London: Henry Kimpton. 1956. Pp. 640. Illus. £6 net.

It is difficult to know for whom this book is designed. The specialist in X-ray diagnosis will find it woefully deficient in treatment of the less commonplace X-ray appearances even of everyday conditions, while many of the illustrations which are present are small and of poor quality. For the student of X-ray diagnosis the book fails in presenting the fundamentals of X-ray interpretation —for example, the normal chest is dismissed in three and a half pages. For

the student also it is much more important to deal with those physical and geometrical factors of projection which enable the shadows to be translated into terms of morbid processes rather than, as Dr. Ritvo does, to describe appearances in various disease processes without regard to the physical significance of the shadows.

If it is primarily for the clinician in diseases of the chest that this book is designed, then, while much of the foregoing holds, the short paragraphs on clinical aspects of the disease which occur in each section are out of place. The physician will not be looking in a volume of this nature for his clinical information.

References are very few. Whole sections, such as that on pulmonary sarcoidosis, carry no references at all, while, with that insularity which is an unfortunate feature of some American authorship, the work of Britain and the Continent is almost wholly ignored.

A. M. RACKOW.

Segment und Lungentuberkulose. By E. HAEFLIGER and G. MARK. Berlin, Gottingen, Heidelberg: Springer-Verlag. 1956. Pp. v+217. Illus.

Segments are not anatomically separated from each other; they represent pulmonary areas supplied by a particular bronchus. Foci of any kind are, therefore, bound to start in one or other segment to which they may or may not remain confined. Examples of many kinds are demonstrated in this book and the collection of X-ray pictures in well-designed three-dimensional diagrams is praiseworthy.

The modern concept of the anatomy and function of the bronchial tree and the respiratory tissue precedes the special parts of the book in well-written chapters.

The exhaustive contents of the book will appeal to everybody interested in the anatomy and pathology of the lung.

S. ENGEL.

Tagungsbericht Zum 7. Kongre B der Suddeutschen Tuberkulosegesellschaft Zusammen mit den Südwestdeutschen Kinderärzten in Lindau (10-12 Juni 1955). Edited by H. BRUGGER. Stuttgart: Georg Thieme Verlag. 1956. Pp. 99. DM. 6.

The collected papers read at a joint meeting of specialists for tuberculosis and pædiatrics present a valuable contribution to the knowledge and study of tuberculosis, especially in childhood. It is gratifying to see that one of the main reports (by Professor Brugger) deals critically with the interpretation of opacities in X-ray films of the chest.

S. ENGEL.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues.

Interesting Cases and Pathological Considerations. By F. Parkes Weber. London: H. K. Lewis and Co. Ltd. 1956. Pp. iv+77. Illus.

Tuberculosis in Obstetrics and Gynæcology. By George Schaefer. London: J. and A. Churchill Ltd. 1956. Pp. xvi+307. Illus. 63s. net.

Postural Drainage. By E. Winifred Thacker. London: Lloyd-Luke. 1956. Pp. viii+56. Illus. 8s. 6d. net.

The Lung as a Mirror of Systemic Disease. By Eli H. Rubin. Oxford: Blackwell Scientific Publications. 1956. Pp. xx+288. Illus. 95s.

Tuberculosis Index and Abstracts of Current Literature. NAPT. Vol. 10. No. 2. June, 1956. 25s. per year.

Diagnosis and Treatment of Vascular Disorders (Angiology). Edited by Saul S. Samuels, with 17 contributors. London: Baillière, Tindall and Cox Ltd. Pp. x+622. Illus. 128s.

Cancer of the Lung. By Milton B. Rosenblatt and James R. Lisa. London: Cumberlege, Oxford University Press. 1956. Pp. xiii+330. Illus. 120s. net.

Bronchologie: Technique Endoscopique et Pathologie Trachéo-Bronchique. 2 volumes. By André Soulas and Pierre Mounier-Kuhn. France: Masson et Cie. 1956. Pp. 1,146 (2 volume total). Illus. 14,000 fr.

Tuberkulose-Jahrbuch 1953-54. By R. Griesbach. Berlin: Springer-Verlag. 1956. Pp. VIII+283. Illus. DM. 33.

ANNUAL REPORT OF TORONTO HOSPITAL 1955

Among the observations made in the Annual Report, some extracts of a report on " Recent Trends in the Treatment of Tuberculosis at the Toronto Hospital for Tuberculosis, Weston, Ontario," by Drs. H. S. Coulthard, D. R. Garrett and C. A. Wicks, are of interest.

Rest. Except for patients with bone and joint tuberculosis, most patients on admission who are afebrile and asymptomatic are allowed up to the " bathroom once daily." This exercise category may be amended after the initial examination by the physician, and is frequently increased to " bathroom three times daily " or " full bathroom privileges."

Even for full exercise patients attending the dining room for three meals daily we insist upon a minimum of bed rest as follows: (1) morning rest period with head on pillow for one-and-a-half hours; (2) afternoon rest period with head on pillow for two hours; (3) in bed with lights out at 9.30 p.m.

We continue to use for most patients the following three agents concurrently in the dosage schedule as shown opposite each agent.

Streptomycin—1 g. intramuscularly twice weekly.
PAS—10 g. (14 g. of the sodium PAS) orally daily (in three divided doses).
Isoniazid—300 mgm. orally daily (in three divided doses).

It is recognised that concurrent administration of the three most useful antimicrobial agents in tuberculosis is not practised at many centres because of the understandable desire on the part of many clinicians to reserve at least one of such agents for use if and when deemed necessary.

We are not yet fully convinced that significant resistance does develop with concurrent three drug therapy to a degree making this " triple drug " therapy inadvisable—and we are not at all certain that such resistance reported by the laboratory necessarily involves a lack of clinical effectiveness paralleling the reported resistance.

We give serious attention to the selection of chemotherapy immediately prior to operation and in the post-operative period, particularly for those patients from whom we recover tubercle bacilli resistant to one or more of the agents being used up to the time of operation. In this connection we have used various combinations of antimicrobial agents as an " umbrella " during the operative and post-operative period.

Collapse Therapy. The use of collapse therapy (artificial pneumothorax, artificial pneumoperitoneum and thoracoplasty) at this sanatorium has continued to decline during the past year.

Surgery. Pulmonary resection for residual cavitation and residual large necrotic tuberculous foci in the lung following six to nine months of conservative treatment with rest and chemotherapy has continued to be recommended during the past year. However, with accumulating evidence in recent years regarding the effectiveness of long-term chemotherapy we have felt more confident in certain cases to regard such chemotherapy as definitive treatment without resecting small circumscribed residual necrotic tuberculous foci which in previous years we might have considered it necessary to resect.

Duration of Treatment. In 1952 we began thinking of adequate chemotherapy as being approximately twelve months in duration. In 1953 we extended the prescribed period of chemotherapy in many cases up to fifteen or eighteen months (and in some cases to twenty-four months). The latter duration was rather commonly prescribed for those patients who would be discharged from sanatorium without having their residual tuberculous lesion resected. In 1954 and 1955 we continued to prescribe-long term " three drug " chemotherapy. At the present time, for all patients with active tuberculous disease, chemotherapy is commenced shortly after admission (after a number of specimens have been obtained if possible for laboratory examination). This chemotherapy is continued, and whether or not supplemented by surgical procedures, the patient is almost always sufficiently well clinically to be attending the dining room for three meals daily (full exercise) by the twelfth to fourteenth month after admission.

During 1954 and 1955 we would estimate that the average duration of chemotherapy prescribed for patients was approximately sixteen months (varying from twelve months for minimal pulmonary tuberculosis to twenty-four months or somewhat longer in a few cases for more advanced tuberculosis particularly where resection is not to be done).

Relapse Rates. There is a growing impression at this sanatorium that the relapse rate, at least as far as it can be observed up to this time, has shown a rather significant decrease in respect of those patients who were discharged with medical consent after what we now consider to be adequate treatment. By " adequate treatment " we mean at least one year and preferably fifteen to eighteen months of chemotherapy with surgical treatment if recommended and with discharge from sanatorium upon medical advice. It is possible of course that what we are observing is merely a delay in the reactivation of tuberculous disease following discharge from sanatorium. It is obvious that a study of the relapse rates among patients discharged from sanatorium in the manner described above would be informative at this time.

NOTES AND NOTICES

XIVth INTERNATIONAL CONFERENCE ON TUBERCULOSIS

This conference, under the auspices of the International Union against Tuberculosis, and of the Tuberculosis Association of India, is being held at New Delhi from January 7-11, 1957. The scientific sessions of the conference will be discussing:

Section I. Diagnostic and Biological Problems of Isoniazid Resistant Tubercle Bacilli.

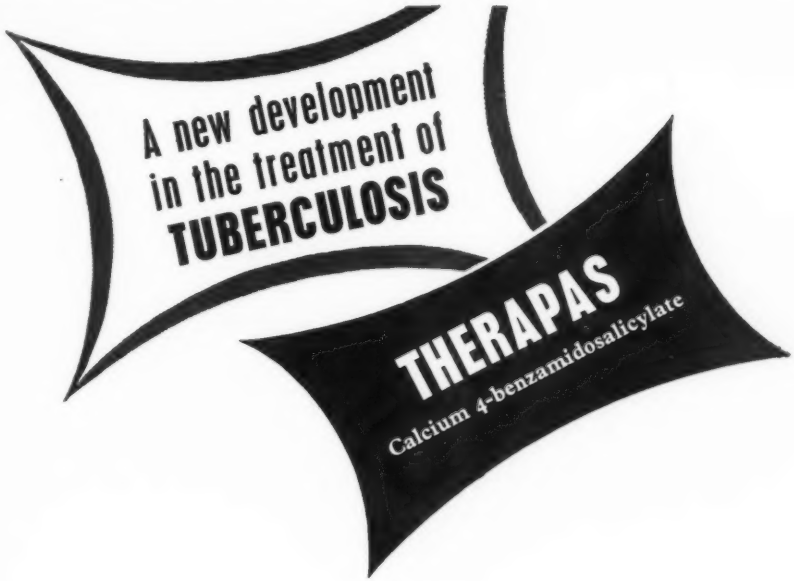
Section II. Clinical and Epidemiological Results of Ambulatory Chemotherapy in Pulmonary Tuberculosis.

Section III. The Incidence of Tuberculosis in Economically Under-developed Countries and the Methods for evaluating it.

Section IV. Symposia including the following subjects:

(1) Value of Tuberculin Reactions for the Selection of Cases for B.C.G. Vaccination and Significance of Post-Vaccination Allergy.
(2) The Importance of Nutritional Factors in Tuberculosis.
(3) Cortisone in the Treatment of Tuberculosis.
(4) Role of Voluntary Tuberculosis Associations in Tuberculosis Control Programme.

Leading authorities on tuberculosis from all over the world will be present at these discussions.



THERAPAS first synthesized in our laboratories in 1951, was introduced into tuberculosis therapy as an alternative to P.A.S. Detailed pharmacological studies have been published in this country (1), and Swiss workers have produced evidence (2) that calcium 4-benzamidosalicylate has a therapeutic action *per se*.

Therapas delays the emergence of streptomycin resistance. Its value in the treatment of genito-urinary tuberculosis is well established (3), (4), (5). Unlike P.A.S. (to which it is converted in the body) it has a slightly sweet, not unpleasant taste.

Effective though **Therapas** has been in these respects, it now appears from recent work (6), that it is of still greater importance. The results indicate that:

Therapas, in combination with isoniazid or streptomycin, gives satisfactory clinical and radiological results in the treatment of pulmonary tuberculosis.

Therapas is just as effective as P.A.S. in delaying the emergence of resistance to either isoniazid or streptomycin.

Therapas can be used wherever P.A.S. is indicated, and is better tolerated.

Dosage: **Therapas** may be administered in daily doses of 14 G.
Availability: Individual packets of 3.5 G. in boxes of 100 packets. 1.0 G. Cachets in containers of 100 and 500. Bulk powder in containers of 100 G. and 500 G.

(1) Bavin, E. M. & James B., *J. Pharmacy & Pharmacol.*, 1953, **5**, 849.

(2) Schonholzer, G., Lauener, H. & Hurni, H. *Schweiz. Med. Wschr.*, 1955, **85**, 222.

(3) Gow, J. C., *Brit. Med. J.*, 1953, **1**, 95.

(4) Ross, J. C., Gow, J. C. & St. Hill, C. A., *Brit. Med. J.*, 1953, **1**, 901.

(5) Ross, J. C., Gow, J. C. & St. Hill, C. A., *Lancet*, 1955, **1**, 116.

(6) Gibson, M. O. J. & Nagley, M. M. *Tubercle, July* 1955, 36, 209.

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